Cardiovascular disease and ethnicity

Focus on the high risk of CVD among South Asians living in Norway and New Zealand

Kjersti Stormark Rabanal

Dissertation for the degree of philosophiae doctor (PhD)

at the University of Oslo

2018

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo

Contents:

Papers 1-3

Appendices

Acknowledgements

I would like to express my deepest gratitude to my main supervisor Professor Haakon E Meyer and co-supervisor PhD Randi M Selmer. They have both inspired me with their knowledge in the field of epidemiology, and given me tremendous support during these years.

Haakon's dedication, knowledge and experience in the fields of epidemiology, cardiovascular disease and immigrant health has been essential for my learning and for the progress in this project. I want to thank Haakon for keeping me "on track "with his exceptional ability to keep the perspective and to keep focus. I am very grateful to Haakon for giving me the opportunity to work on this project, and also for introducing me to our collaborators in New Zealand.

Randi's contributions to this project have also been invaluable. I want to thank Randi for sharing her experience and knowledge within the fields of cardiovascular disease, epidemiology and statistics in a comprehensible and inspiring way. Her guidance on the statistics and methodological issues was deeply appreciated. I have been very fortunate to have her on my team.

Warm thanks to Grethe S Tell, project leader of the CVDNOR project, and to Jannicke Igland, senior engineer at the University of Bergen for their constructive comments and much appreciated contributions. It has been a privilege for me to work with both Grethe and Jannicke, and to get to work with the nationwide CVDNOR data. I am also very thankful for the significant help I got from Jannicke despite her own busy schedule while I was working with the CVDNOR data.

I would like to thank our New Zealand collaborators; Rod Jackson, Romana Pylypchuk and Suneela Mehta, who I was so lucky to be able to work with and to learn from. I am very grateful that I got to work with the PREDICT data, for getting the opportunity to visit Rod Jackson and his team in New Zealand, and for all their valuable contributions to my papers. I am impressed by the way Rod Jackson and his team at the University of Auckland have managed to implement cardiovascular prediction models in clinical practice in such a large scale, and simultaneously collect important research data.

Summary

Background

The burden of cardiovascular disease (CVD) differs between ethnic groups. Information from Norwegian health studies has shown that immigrants from South Asia have a high prevalence of diabetes, abdominal obesity, high levels of triglycerides and low levels of HDL. This is in agreement with international studies reporting a high risk of CVD in South Asian populations, particularly coronary heart disease (CHD). The incidence and mortality of CVD has, however, not been studied among immigrants in Norway. Our knowledge about cardiovascular risk factors is largely based on information from European populations, and very few studies have examined the prospective relationship between conventional risk factors and later CVD in populations of other ethnic backgrounds. Total risk prediction models are recommended by international guidelines to inform treatment decisions in clinical practice, and should be externally validated. We are only aware of one study that has formally validated existing cardiovascular risk score models with measures of discrimination and calibration in South Asians.

Objectives

The overall aim in this project was to study the burden of CVD among immigrants in Norway, and to study the prospective relationships between major risk factors and subsequent CVD among South Asians and Europeans. Our specific aims were:

1. To describe the burden of acute myocardial infarction (AMI) and stroke in immigrant groups living in Norway (paper 1).

2. To prospectively study the relationship between conventional risk factors and later CVD in South Asians compared with Europeans in Norway and New Zealand, and to study to what extent the risk factors could explain any possible differences in the risk of first CVD events between the ethnic groups (paper 2).

3. To examine the validity of the Framingham cardiovascular risk score for predicting risk of CVD in South Asians compared with Europeans (paper 3).

4. To assess the additional role of obesity and social deprivation on the risk of CVD in South Asians compared with Europeans (paper 3).

Subjects and methods

Data for paper 1 came from the Cardiovascular Disease in Norway (CVDNOR) project which enabled us to study the whole Norwegian population during 1994-2009. Information about CVD outcomes

were obtained from all Norwegian hospitals and the Cause of Death Registry. Country of birth was used to indicate ethnicity. We calculated age-standardized AMI and stroke event rates and used Poisson regression to calculate rate ratios (RRs) with ethnic Norwegians as reference. In paper 2, we used information from a New Zealand (PREDICT) and a Norwegian (CONOR) cohort. Cox regression was used to study the prospective relationships between major cardiovascular risk factors and subsequent CVD events identified through hospital and mortality data for South Asians and Europeans in both countries. Cox regression was also used to study the contribution of the conventional risk factors for the increased risk of CVD in South Asians versus Europeans. In paper 3, we used an updated version of the New Zealand PREDICT cohort and included participants of Indian and European self-reported ethnicity. We examined the discriminative abilities of the Framingham 5- year risk score using the area under the receiver operating characteristics curve and calculation of Harrell's C. We measured calibration graphically in a plot of predicted minus observed event rates (life table) within deciles of predicted risk. Cox regression was used to study the role of body mass index and social deprivation with and without adjustment for the Framingham risk score.

Main results

In paper 1, we found that immigrants in Norway vary in risk of CVD. South Asians had a marked increase of both AMI and stroke compared to those born in Norway. Immigrants from Former Yugoslavia had increased risk of AMI, and Former Yugoslavian men also had increased risk of stroke. The lowest risk of AMI was seen in East Asians. The excess risk of CVD in South Asians compared with Europeans was reconfirmed in paper 2 and paper 3. In paper 2, we found that the major risk factors were positively associated with subsequent risk of CVD in South Asians and in Europeans in both New Zealand and Norwegian data. We also found that diabetes and total cholesterol (TC)/high-density lipoprotein (HDL) ratio explained some of the excess risk of CVD in South Asians. The Framingham risk prediction model predicted the 5-year risk of CVD reasonably well in Indian men in New Zealand, while it overestimated risk in Indian women and in European men and women. BMI and social deprivation could be useful predictors in addition to a Framingham cardiovascular risk score.

Conclusion

There are large variations in risk of CVD among immigrants in Norway. South Asians had a particularly high risk of both AMI and stroke compared with Norwegian-born. A high risk of CVD was also found among Indians in New Zealand compared with Europeans. The major risk factors

systolic blood pressure, TC/HDL ratio, smoking and diabetes are positively related to later CVD in South Asians as in Europeans. The high prevalence of diabetes in South Asians is of particular concern in both Norway and New Zealand as it appeared to partly explain the excess risk of CVD in South Asians. Available risk scores should be externally validated, and we have shown that a well-known cardiovascular risk prediction model performed well in Indian men, but overestimated the 5-year risk in Indian women and in European men and women.

List of papers

1. Rabanal KS, Selmer RM, Igland J, Tell GS, Meyer HE. Ethnic inequalities in acute myocardial infarction and stroke rates in Norway 1994-2009: a nationwide cohort study (CVDNOR). BMC Public Health. 2015;15:1073.

2. Rabanal KS, Meyer HE, Tell GS, Igland J, Pylypchuk R, Mehta S, Kumar B, Jenum AK, Selmer RM, Jackson R. Can traditional risk factors explain the higher risk of cardiovascular disease in South Asians compared to Europeans in Norway and New Zealand? Two cohort studies. BMJ Open 2017;7(12):e016819.

3. Rabanal KS, Meyer HE, Pylypchuk R, Mehta S, Selmer RM, Jackson R. Performance of a Framingham cardiovascular risk model among Indians and Europeans in New Zealand and the role of body mass index and social deprivation. Open Heart 2018;5:e000821.

Terms and abbreviations

Terms

Country of birth	Country of birth mainly refers to the mother's place of residence at the time she's giving birth, as defined by Statistics Norway (Norwegian data).
Ethnic Norwegians	The term "ethnic Norwegians" refers to persons born in Norway (synonym to "Norwegian-born"). The term is mainly used in paper 1.
European	Refers to natives of Europe. Other words from the literature which are usually used with the same meaning may be "White", "Caucasian" or "White of European origin". Caucasian is not used here since it has been recommended to abandon the concept (1, p. 38).
Immigrant	In paper 1, this term refers to persons who were born in a country outside Norway with either one or both parents born abroad (95% of all the immigrants and 99.8% of the South Asian group in paper 1 had both parents born abroad and four foreign-born grandparents).
	Statistics Norway defines immigrants as persons born abroad of two foreign-born parents and four foreign-born grandparents.
Norwegian-born	Persons who were born in Norway. As for country of birth, this is usually defined by the mother's place of residence when giving birth.
South Asian	Refers to persons with their ancestry in the Indian subcontinent, including countries such as India, Pakistan, Sri Lanka, Bangladesh, Nepal and Bhutan.

Abbreviations

AF	Atrial fibrillation
AMI	Acute myocardial infarction
ASVD	Arteriosclerotic vascular disease
AUC	Area under the receiver operating characteristics curve
BMI	Body mass index
CHD	Coronary Heart Disease
CONOR	Cohort of Norway
CV	Cardiovascular
CVD	Cardiovascular disease
CVDNOR	The Cardiovascular Disease in Norway project
DALY	Disability Adjusted Life Years, described in footnote page 11
eGFR	Estimated glomerular filtration rate
GBD	Global Burden of Disease
HDL	High-density lipoprotein
HF	Heart Failure
HR	Hazard ratio
ICD	International Classification of Diseases
PERM	Percentage of Excess Risk Mediated
PREDICT	PREDICT mainly refers to the PREDICT Cardiovascular Disease Cohort in New Zealand Primary Care. In some cases (when indicated). PREDICT may also refer to the web-based clinical tool used to gather information for this cohort through New Zealand primary care.
NZ	New Zealand
ROC	Receiver operating characteristics curve
RR	Rate ratio
SBP	Systolic blood pressure
TC	Total cholesterol
TIA	Transient Ischemic Attack
UK	United Kingdom
US	United States, refers to The United States of America
WHO	World Health Organization
WHR	Waist to hip ratio
YLL	Years of Life Lost, described in footnote page 11

1.0 General introduction

In this section, I mainly review the literature with a special focus on the knowledge about South Asian populations (persons originating from countries in the Indian subcontinent, such as India, Pakistan, Sri Lanka and Bangladesh) prior to the present studies.

1.1 Cardiovascular disease (CVD)

Cardiovascular diseases (CVD) are the diseases of the heart and blood vessels, and includes coronary heart disease (CHD), cerebrovascular disease, heart failure and peripheral arterial disease. Myocardial infarction (MI) (a sub-category of CHD) and stroke are two major manifestations of CVD mostly caused by occlusion of the blood flow to the heart or brain. Stroke can also be caused by bleeding from one of the blood vessels supplying the brain (haemorrhagic stroke) (2). The two main pathological processes behind CVD are atherosclerosis and thrombosis. The former involves stiffening and thickening of the arterial wall as well as the accumulation of lipids and fibrous elements in the arteries forming atherosclerotic plaques, while the latter involves pathological blood clot formation with over-activated haemostasis in the absence of bleeding (3-5). Atherosclerosis develops over many years and is an inflammatory disease of the wall of the arterial blood vessels (6, 7). The pathophysiological mechanisms behind atherosclerosis are complex and involves immunological responses from the arterial wall cells when being exposed to damaging stimuli (7, 8). A range of different factors can cause damage and promote atherosclerosis including known cardiovascular risk factors (7). Atherosclerotic cardiovascular events are often manifested via a thrombotic event (9). Thrombosis may generally be induced by defects in the endothelium, altered blood flow or changes in blood constituents (4). Fibrinogen, coagulation factor VII, factor VIII and von Willebrand factor are examples of haemostatic factors that can promote thrombosis (4, 9).

1.1.1 Cardiovascular risk factors

Underlying determinants

The underlying determinants or "the causes of the causes" of CVD are the demographic, socioeconomic, cultural and environmental circumstances surrounding the individual (2, 10). Major forces like globalization, urbanization, population ageing and migration are thus important determinants of cardiovascular health (2).

Conventional risk factor

In addition to age and sex, the major CVD risk factors are high blood pressure, smoking, dyslipidaemia, and diabetes (11). These risk factors are highly related to lifestyle as most of them are influenced by individual behaviour. Unhealthy diet, physical inactivity, tobacco use as well as harmful use of alcohol are the most important behavioural risk factors (2). As these risk factors are well- established they will only be discussed further in regard to South Asian populations.

The role of conventional risk factors in South Asians

Our understanding of cardiovascular risk factors is mainly based on studies performed in populations of European descent. When we planned the present study, only two prospective studies of our awareness, had studied the prospective relationship between risk factors and subsequent CVD in South Asian populations (12, 13). Both studies reported hazard ratios (HRs) for the risk factor- outcome relationship among South Asian migrant populations living in the United Kingdom (UK) compared with Europeans, and found that traditional risk factors had similar relationships with the outcome (CHD mortality) in both ethnic groups (12, 13). Two large and multinational case-control studies have also *retrospectively* studied the effect of potentially modifiable risk factors for MI (the INTERHEART study) (14) and stroke (the INTERSTROKE study) (15) in different countries around the world. The INTERHEART and INTERSTROKE studies found that the relationships between risk factors and CVD were similar in the different populations and that nine-ten risk factors account for most of the risk of MI and stroke worldwide (14, 15). A case-control study from Bangalore, India, also indicate that the traditional risk factors are important for the risk of MI in Indians living in urban India (16, 17).

During our work with the present study, two additional prospective studies have emerged supporting the notion of similar relationships between cardiovascular risk factors and later CVD among South Asian immigrants living in the UK compared with Europeans (18, 19). Two other studies from the UK also recently emerged reporting the relationship between prediabetes and later CVD (20), and the association between different measures of blood pressure and subsequent stroke (21). The latter study found indications of a stronger association between blood pressure and the risk of stroke in South Asians versus Europeans (21). Table 1 gives an overview of all the prospective studies reporting the relationship between major risk factors (high blood pressure, smoking, dyslipidaemia and/or diabetes) and later CVD in South Asian populations that I was able to find using pragmatic searches.

Table 1. Prospective studies reporting the association between major cardiovascular risk factors and subsequent CVD in South Asian populations

Author and date, (ref)	Sample	Sex-specific analyses	Name of study/source and time of baseline collection	Number of persons and CVD cases	Effect measure	CV outcome	Risk factors	Main findings in this context
Forouhi et al. 2006, (12)	South Asian and European men, 40-69 years at baseline	Yes, the study only included men	The population-based Southall and Brent studies (London) between 1988 and 1991. Followed to 2006.	South Asians, n=1420 (108 CHD deaths) Europeans, n=1787 (94 CHD deaths)	HRs from Cox regression	CHD death	Age, smoking, occupation, education, BMI, waist circumference, hypertension, lipids, blood glucose, insulin resistance, diabetes and metabolic syndrome	The major risk factors (smoking, hypertension, lipids and diabetes) were similarly related with the outcome in both ethnic groups. The excess risk in South Asians was also confirmed.
Williams et al. 2011, (13)	South Asian and White British men and women, ≥35 years at baseline	No, combined analyses – adjusted for sex	Data from Health Survey for England, 1999 and 2004. Followed to 2008.	South Asians, n=2120 (33 CHD deaths) White British, n=13293 (195 CHD deaths)	HRs from Cox regression	CHD death	Age, gender, BMI, hypertension, diabetes, smoking, physical activity, education, occupation and income	Major risk factors (hypertension, diabetes, smoking) were similarly related with the outcome in both ethnic groups
Beginning of the present study								
Tillin et al. 2013, (18)	South Asian, European and African Caribbean men and women, 40-69 years at baseline	No, combined analyses – adjusted for sex	The SABRE (Southall and Brent Revisited) study, 1988–1991. Followed to 2011.	South Asians, n=1517 (599 CHD events, 157 stroke events), Europeans, n=2049 (551 CHD events, 173 stroke events) African Caribbean, n=630 (105 CHD events, 71 stroke events)	SHRs from competing risks regression	CHD and stroke (fatal and non-fatal)	Smoking, diabetes, SBP/treated hypertension, BMI, WHR, waist to thigh ratio, blood lipids, blood glucose and measures of insulin resistance, alcohol consumption, fruit and vegetables consumption, physical activity, education, occupation	The main focus was on ethnic differences in CHD and stroke, and whether adjustment for metabolic risk factors would attenuate these differences. The authors concluded that ethnic differences in measured metabolic risk factors did not explain differences in coronary heart disease incidence. Meanwhile, diabetes seemed to be more predictive of stroke in the competing risk regression in both African Caribbean and South Asians

3

								than in Europeans.
Eriksen et al. 2015, (19)	South Asian and European men and women, 40-69 years at baseline	No, combined analyses – adjusted for sex	The Southall arm of the SABRE study, 1988-1990. Followed to 2011.	South Asians, n=1006 (346 CVD events), Europeans, n=1090 (255 events)	HRs from Cox regression	CVD, CHD	Smoking, alcohol intake, physical activity, fruit and vegetable intake	Behavioural risk factors (smoking, alcohol intake, inactivity and infrequent fruit and vegetable intake) were similarly related with the outcome in both ethnic groups.
Eastwood et al. 2015, (20)	South Asians and Europeans, 40-69 years at baseline	No, combined analyses – adjusted for sex	The SABRE (Southall and Brent Revisited) study, 1988-1991. Followed to 2011.	South Asians, n=1139 (478 CVD events), Europeans, n=1336 (423 CVD events)	SHRs from competing risks regression	CVD, stroke and CHD	Prediabetes and diabetes	Diabetes seemed to be similarly related with CVD, CHD and stroke in both ethnic groups. Results for prediabetes will not be elaborated here.
Eastwood et al. 2015, (21)	South Asian and European men, 40-69 years at baseline	Yes, the study only included men	The SABRE (Southall and Brent Revisited) study, 1988-1991. Followed to 2011.	South Asians, n=1074 (102 stroke events), Europeans, n=1375 (104 stroke events)	Odds ratios from logistic regression (Cox regression was not used due to violations of the proportional hazards assumptions)	Stroke	Different blood pressure measurement: SBP, DBP, PP and MAP	SBP, DBP and MAP were more strongly associated with stroke risk in South Asians than in Europeans.

BMI, body mass index; CHD, Coronary Heart Disease; CV; Cardiovascular; DBP, diastolic blood pressure; HR, Hazard ratio; MAP, mean arterial pressure; SBP, systolic blood pressure; SHR, Subhazard ratio; WHR, waist to hip ratio

Overweight/obesity as a risk factor for CVD

Having a high body mass index (BMI) is a risk factor for CVD (22). The association between BMI and CVD is U- or J-shaped (23-25) with the lowest risk between BMI-values of 18.5-24.9 kg/m^2, and an increased risk of CVD at BMI-levels below 18.5 kg/m^2 and from 25 kg/m^2 and above. The World Health Organisation (WHO) categorises overweight as BMI ≥25 kg/m^2 and obesity as BMI ≥30 kg/m^2 (26). These categorisations are intended for international use. However, Asian populations generally have a higher percentage of body fat, more metabolic disturbances and cardiovascular risk factors than those of European origin of the same age, sex, and BMI (27-29). In 2004, a WHO expert consultation therefore identified lower public health action BMI cut-offs intended for Asian populations (27). The consultation concluded that the available data did not indicate one clear BMI cut-off point for all Asians for overweight or obesity, and provided suggestions about how the respective countries could make decisions about definitions of increased risk for their population. The suggested categories for public health action for Asian populations by the WHO expert consultation of 2004 were: <18.5 kg/m^2 - underweight; 18.5–23 kg/m^2 - increasing but acceptable risk; 23–27.5 kg/m^2 - increased risk; and ≥27.5 kg/m^2 - high risk (27). In 2009, the Indian Consensus Group also studied the available evidence and defined BMI of 23-24.9 kg/m^2 as overweight and ≥25 kg/m^2 as obesity for Asian Indians (30). These cut-offs have been widely used by physicians in India although the issue is still controversial, partly because of the lack of robust data (28).

The effect of BMI on CVD is, at least to some extent, mediated through the risk factors high blood pressure, dyslipidaemia and diabetes (24, 31, 32). Some obese patients, however, do not show high levels of these risk factors or other factors that are usually associated with obesity, and are sometimes referred to as "healthy obese" individuals resistant to some of the metabolic adversities related to obesity (33). Whether obesity is a cardiovascular risk factor independent of the classical risk factors has therefore been questioned (33, 34). Several studies, however, point to a remaining risk of BMI after taking classical risk factors into account (35, 36). Also, the long-term results from the Whitehall study with follow-up over two decades, support that healthy obesity is a transient state before progressing to a more unhealthy state with metabolic abnormalities (37). On the other hand, although BMI-levels have increased in the Norwegian population for both genders during the last 30- 40 years (38-40) the CVD mortality has decreased substantially during the same time period (41).

South Asians in different countries have high levels of abdominal obesity, usually measured by waist to hip ratio (WHR) or waist circumference, compared with Europeans and several other ethnic groups (42-44). This also applies to South Asians in Norway and New Zealand (45, 46). Because South Asians also appear to have increased risk of diabetes and metabolic disturbances at lower

levels of abdominal obesity, the International Diabetes Federation (IDF) has suggested to use a lower cut-off of waist circumference as a measure of central obesity for South Asian men (≥ 90 cm) versus European men (≥ 94 cm). For European and South Asian women, the cut-offs are currently the same (≥ 80 cm) (47). The IDF underlines that these cut-offs are pragmatic, and that better data is needed in order to link them to risk. The INTERHEART study which covers 52 countries representing all inhabited continents, found that waist-to-hip ratio was the strongest anthropometric predictor of MI (48). This was found in both genders, in all the ethnic groups, in smokers and non-smokers, and in persons with or without dyslipidaemia, diabetes or hypertension.

Socioeconomic position and deprivation in relation to CVD

Health inequalities according to social position have been documented for centuries (49). Until the 1970's, CHD was considered to be a disease of affluence caused by stress and an affluent lifestyle (50). Studies from the United States (US) and the UK had shown that this was true for men in the 1930's and 1940's (51, 52). The Whitehall study among civil servants in London in the late 1970's, however, demonstrated that the social gradient had been reversed in British men (53, 54), this was also seen in the US (55). This meant that lower CHD mortality was now associated with higher social positions. A social gradient in cardiovascular health where better health is enjoyed by men and women of higher socioeconomic positions (often indicated by income, education or occupation) is now well-known and have been demonstrated in many high-income countries such as Canada, the US, Norway and New Zealand (52, 53, 56-60). Furthermore, the social gradient implies that health differences do not merely exist between the rich and the poor, but that the health status improves for each step on the socioeconomic ladder (50).

The socioeconomic gradient is not necessarily present or identical among all subgroups, such as ethnic minority groups. Findings for different groups of immigrants have been somewhat conflicting (61-63), and earlier studies from the UK and the Netherlands did not find a relationship between socioeconomic position and CVD in some of the ethnic minority groups that were studied (Turkish and Moroccan men and women in the Netherlands; South Asians in the UK) (63, 64). The lack of a (or a weak) social gradient in health among some of the immigrant groups corresponds with observations in low- and middle income countries that many of the immigrants descend from (65, 66). Also, researchers in the US has suggested that Mexican migrants "import" their weak or flat social gradients from Mexico and found partial support for this hypothesis in one of their studies (67). The idea that weak or flat social gradients among immigrant groups reflect the social gradients in their (low- or middle income) countries of birth corresponds with the "diffusion of innovation"

theory (68, 69). This diffusion theory suggests that the increased burden of CHD first affected those in the higher socioeconomic positions in high-income countries because they were the first to afford the unhealthy lifestyles (smoking, diets rich in saturated fats and physical inactivity). After some time, the diseases started to spread to the lower socioeconomic groups and to poorer countries partly as a consequence of increased living standards (as some unhealthy behaviours require a minimum level of income) among these groups and countries, but also as a result of imitation. When the CHD epidemic started to decline, the high socioeconomic group was again the first to benefit as people belonging to this group had been the first to adopt healthy behaviours (quit smoking, start to exercise and eat healthier) (68, 69). Recent nationwide registry-studies from the Netherlands found similar socioeconomic gradients in cardiovascular health (stroke and AMI) among several immigrant groups as for the Dutch majority population, especially for AMI (70, 71). The researchers pointed out that this was in line with the diffusion of innovation theory as it might indicate that the immigrants are converging towards the majority population when it comes to socioeconomic inequalities in health (70, 71). This has not been studied on a large scale in Norway so far, but a previous study has examined the association between self-reported socioeconomic status and self-reported health (self- rated health, prevalence of diabetes and distress) among Pakistanis in Norway compared with ethnic Norwegians (72). The study used data from the Oslo Health Study 2000-2001 and found an inverse association between socioeconomic factors and health among the ethnic Norwegian group, but not in the Pakistani group (72). Another study, which also used data from the Oslo Health Studies 2000-2002 (including the part aimed at immigrants), found an inverse relationship between high education and the probability of smoking among men from all immigrant groups in the study except for men from Sri Lanka (73).

In addition to socioeconomic indicators on the individual level (such as income, education and occupation), area-based measures also exist (74, 75). These are usually aggregated from individual or small area data and are often based on census or other administrative databases (74). These area- based measures can be used to characterise a living area on a continuum from deprived to affluent. According to Peter Townsend, a well-known British sociologist, relative deprivation can be defined as "a state of observable and demonstrable disadvantage relative to the local community or the wider society or nation to which an individual, family or group belongs" (76, p. 125). Area-based measures are sometimes used as a proxy to individual socioeconomic position, when individual measures are not available. However, area-based measures relate to areas and not to individuals, and they capture both compositional and contextual effects of material and social circumstances (77).

1.1.2 Total cardiovascular risk prediction

The Framingham Heart Study was the first well-constructed longitudinal cohort study to investigate and identify cardiovascular risk factors (78). The Framingham Heart study has contributed with important information about cardiovascular risk factors and Framingham researchers discovered that risk factors actually *precede* the development of disease (78). The Framingham researchers were also pioneers in constructing multivariable risk models to predict an individual's total risk of CVD based on information from several risk factors (78). Because cardiovascular risk factors interact with each other, it has been suggested that moderate reductions in several risk factors could be more effective for risk reduction instead of large reductions in one risk factor (79). A total risk approach to primary prevention of cardiovascular disease is currently recommended in different countries around the world (80-82).

Most existing prediction models are based on information from European populations. As stated in the introduction of paper 3, cardiovascular risk models should be externally validated in the population it is applied to, to assure that they are clinically useful (83). Few studies have validated existing models in South Asian populations. A pragmatic search using different combinations of the following search terms "South Asians", "risk score", "cardiovascular", "predicted risk" and "ethnic" yielded four prospective follow-up studies, two retrospective case-control studies and one cross-sectional study focusing on the performance of cardiovascular risk scores among South Asians. These are summarized in Table 2. Although all were focusing on the performance of cardiovascular prediction models, only one of the studies reported measures of discrimination and calibration (84). A cross-sectional study from the US focused on subclinical atherosclerosis instead of clinical cardiovascular events (85) applying data from a relatively young cohort study called the Mediators of Atherosclerosis in South Asians Living in America (MASALA) (86).

An Indian research protocol published last year (2017) indicates that a validation of a Framingham risk score as well as the development of a new risk prediction score based on samples from urban and rural parts of India are underway (87).

Table 2. Overview of the available studies to have externally validated or focused on the performance of existing cardiovascular risk scores in South Asian populations

Author and date, (ref)	Sample	Study design	Country	Number of persons and CVD cases	CV outcome	Risk score	Main findings in this context
Guha et al. 2004, (88)	Cases were patients first time presented with ACS without previous CHD and with available medical records, aged 32-76 years. Controls were selected from outpatient department without any cardiovascular symptoms or history, aged 33-75 years.	Retrospective case-control study	India	252 cases and 212 age and sex matched controls	ACS	Framingham 10-year	Among non-diabetic patients, the mean predicted risk was higher in patients than in controls (14.2% vs 8.6%, p<0.01). In diabetic patients, no significant difference in predicted risk between patients and controls were found (11.4% vs 10.4%, p>0.05)
Bhopal et al. 2005, (89)	Men and women aged 25-74 years. South Asians screened between May 1995 and March 1997.	Prospective cohort study (median follow-up time for the preliminary analyses of mortality was 7.1 years for South Asians)	The UK	South Asians, n=576, 19 CHD deaths and 3 stroke deaths. Europeans, n=725, 22 CHD deaths and 9 stroke deaths	Expected CHD and stroke deaths (based on published SMRs and preliminary analyses of mortality in the Newcastle Heart Project sample population).	Framingham, SCORE, FINRISK (all models predicted 10-year risk)	The FINRISK and Framingham risk scores gave similar results that corresponded with the published SMRs and the preliminary analyses of mortality in the New Castle Heart project sample population. The SCORE model did not correspond with the high risk of CHD and stroke mortality in South Asians.
Jaquet et al. 2008, (90)	Caribbean Indian patients who were classified as having type 2 diabetes or impaired glucose tolerance in 1997 participating in a second examination in 2006, without CVD prior to 1997.	Longitudinal cohort study (8.5 year follow-up)	Guadeloupe	Caribbean Indians, n=148, 31 CV events	CV outcomes requiring hospitalization (fatal and non-fatal): stroke, angina pectoris, acute CHD, acute PVD	Framingham 10-year	The Framingham risk score was significantly associated with the risk of CVD in Cox-regression analyses, while the metabolic syndrome was not significantly associated with the risk of CVD.
Guha et al. 2008, (91)	Cases were patients first time presented with ACS without previous CHD and with available medical records. Controls were selected from outpatient department without any cardiovascular symptoms or history.	Retrospective case-control study (continuation of Guha et al. 2004)	India	350 cases and 293 age- and sex- matched controls	ACS	Framingham 10-year	Similar as to the previous study in 2004: In non-diabetic patients, the mean predicted risk was significantly higher in patients than in controls (14.1% vs 8.6%, p<0.01). In diabetic patients, there were no significant difference in predicted risk between patients and controls (11.4% vs 10.4%, p=NS)

							Conclusion: a model that better identifies high-risk patients is needed.
Bellary et al. 2010 (92)	South Asians from the United Kingdom Asian Diabetes Study, with type 2 diabetes carried out 2004-2007. White European patients with type 2 diabetes were recruited from 25 general practices, UK. 30-74 years with no history of CVD.	Prospective cohort study (2-year follow-up)	The UK	South Asians, n=1486 (1140 were free of CVD at baseline), 97 CVD cases Europeans, n=492 (317 were free of CVD at baseline), 29 CVD cases	CVD (fatal and non-fatal)	Framingham 10-year and the United Kingdom Prospective Diabetes Study 10-year risk score	The study found a trend for increasing CVD events with increasing predicted risk in both ethnic groups. Despite quite similar predicted CVD risks in the South Asian and the European groups, the CVD rates were higher in the South Asian group suggesting that the risk scores might have underestimated risk in the South Asian group – but this was not tested.
				Beginning of the present study			
Tillin et al. 2014, (84)	Participants aged 40-69 years at baseline (1988-1991) were in the Southall And Brent Revisited study randomly selected from primary care physician lists and workplaces. Participants were revisited 2008-2011.	Prospective cohort study (10-year follow-up)	The UK	South Asians, n=1317 Europeans, n=1803	First CVD events: myocardial infarction, coronary revascularisation, angina, transient ischemic attack or stroke	Modified Framingham 10-year (NICE) and QRISK2 10-year	QRISK2 and Framingham discriminated equivalently and modestly in Europeans of both genders. QRISK2 underestimated the risk in South Asian men, and both scores under-predicted the risk of CVD in South Asian women. Framingham predicted the risk fairly well in Indian men after having added a factor of 1.4 according to NICE guidelines. See the paper for measures of discrimination.
Kandula et al. 2014, (85)	South Asians frm the Mediators of Atherosclerosis in South Asians Living in America Study, 40-79 years and free of atherosclerotic CVD	Cross-sectional	The US	South Asians, n=893	Baseline levels of subclinical atherosclerosis (CAC and CIMT)	The 2013 American Heart Association/ American College of Cardiology Pooled Cohort Equations	The study found associations between subclinical atherosclerosis (CAC and CIMT) at baseline and 10-year and lifetime predicted risk for atherosclerotic CVD among South Asians in the US

ACS, acute coronary syndrome; CAC, coronary artery calcium; CHD, coronary heart disease; CIMT, carotid intima media thickness; CVD, cardiovascular disease; NICE, National Institute for Health and Care Excellence (UK); NS, non-significant; PVD, peripheral vascular disease

1.2 CVD Epidemiology - the global burden

CVDs are the leading causes of death worldwide and have remained so for many years (93, 94). While the burden of CVD has declined in many high-income countries during the last decades, some low- and middle income countries have seen an opposite trend with an increasing burden of CVD (95, 96). The largest share of CVD deaths now occur in low- and middle income countries; in 2008 it was estimated that over 80% of all CVD deaths occurred in these countries (97).

Despite a general lack of good quality data on the burden of CVD in low- and middle income countries (98), the Global Burden of Disease (GBD) study provides estimates of the burden of CVD using different mortality and disability metrics for all regions of the world based on available data sources combined with statistical computing (99, 100). The metrics presented by the GBD study include mortality rates, years of life lost (YLL[1]), disability-adjusted life-years (DALYs[2]) and age-standardized prevalence measures among others (99). The estimated global number of CVD cases in 2015 was 422.7 million. The regional burden vary for the different cardiovascular conditions. For example, Eastern Europe had the highest estimated age-standardized prevalence of coronary heart disease in 2015, followed by Central Asia and Central Europe, while the highest age-standardized prevalence of stroke was found in Oceania, followed by Eastern Europe, Central Asia and Southeast Asia (99). It should be noted that there is limited health data on CVD in some regions of the world despite the available GBD estimates, such as in India and sub-Saharan Africa (99). This means that when data is limited, some of the provided GBD estimates are, to a larger extent based on extrapolations and assumptions rather than real data (101). In India, for example, there is no adequately functional system for the reporting of causes of death, and The Medical Certification of Cause of Death system under the Office of the Registrar General of India only covered 22% of Indian deaths in 2015 (102).

1.2.1 Incidence of CVD in Norway and New Zealand

Recent analyses have shown a decline in the incidence of first acute myocardial infarction (AMI) during 2001-2014 in Norway (103, 104), and improved 28-day and 1-year survival after first AMI

---

[1] The YLL measure is a measure of premature mortality which takes into account the age at which deaths occur, by giving greater weight to deaths at younger age and lower weight to deaths at older age. It is calculated by multiplying the number of deaths with a standard life expectancy for the age the deaths occur.

[2] The DALY measure combines time lost due to premature death and time lived with disability. One DALY can be thought of as one lost year of 'healthy' life. The measured disease burden reflects the difference between a population's health status and the health status of a normative reference population.

during 2001-2009 (105). In those younger than 45 years, a stagnation in the AMI incidence was observed for the years 2001-2009 (104), but after 2009 a decline was also evident in this young age- group (104). A study based on data from three health surveys (carried out in 1994-1995, 2001-2002 and 2007-2008) in Tromsø, Norway, found that the decline in the incidence of CHD was driven by fewer out-of-hospital sudden death and hospitalized ST-segment-elevation MI. Furthermore, the study found that favourable changes in modifiable risk factors accounted for 66% of the decline in CHD events (106). When it comes to stroke, the trend seems to be somewhat different than for CHD with indications from the Tromsø study of an increase during the last three decades for ischemic stroke in women aged 30-49 years, a decline in women aged 50 to 74 years and men aged 65 to 74 years, and no change was found among the oldest (107). Case fatality of ischemic stroke declined in men during the same period, but not in women (107). For intracerebral haemorrhage, the Tromsø study found no significant changes during the last two decades in incidence or case fatality rates (108). The trends in temporal trends in the incidence and case-fatality of stroke has, so far, not been studied on a national basis in Norway. Furthermore, trends in CVD have never been studied among immigrants in Norway.

In New Zealand, the rates of first AMI hospitalisations have declined from 1995-2015 (109, 110). Stroke rates, early case-fatality and 1-year mortality after stroke also declined in the general population in Auckland, New Zealand, from 1981-2012 (111). However, this beneficial development was not seen in all ethnic groups. For example, in Māori and Pacific people, non-significant increases in stroke incidence (first-ever strokes) and attack rates (incident and recurrent strokes combined) were found between the study periods 1981–1982 and 2011–2012 (111). South Asians were not studied explicitly.

1.2.2 CVD mortality and trends in mortality rates

CVDs were responsible for 17.6 million deaths in 2016 according to GBD estimates (93). This is similar to the 2015 WHO Global Health Estimates (GHE) of 17.7 million deaths (31 % of all deaths) (94). The majority (> 85%) of all CVD deaths in 2016 was due to coronary heart disease and cerebrovascular disease (93). While the total global numbers of CVD deaths increased with 14.5% from 2006-2016, the age-standardized death rates *decreased* with the same percentage from 2006-2016 (93). The increase in absolute numbers of CVD deaths was largely due to demographic changes (ageing and growth of populations) while the decrease in age-standardized death rates, to a greater extent, reflects epidemiologic changes in disease (e.g. changes in levels of risk factors) (112). South Asia was the region with the largest estimated increase in CVD deaths in the period

1990-2013 with >1.7 million more deaths in 2013 vs in 1990 (an increase of 97%) (112).

As in many other developed nations, CVD mortality in Norway has steadily declined from the 1970's when it reached its peak after the Second World War and until today (Figure 1).
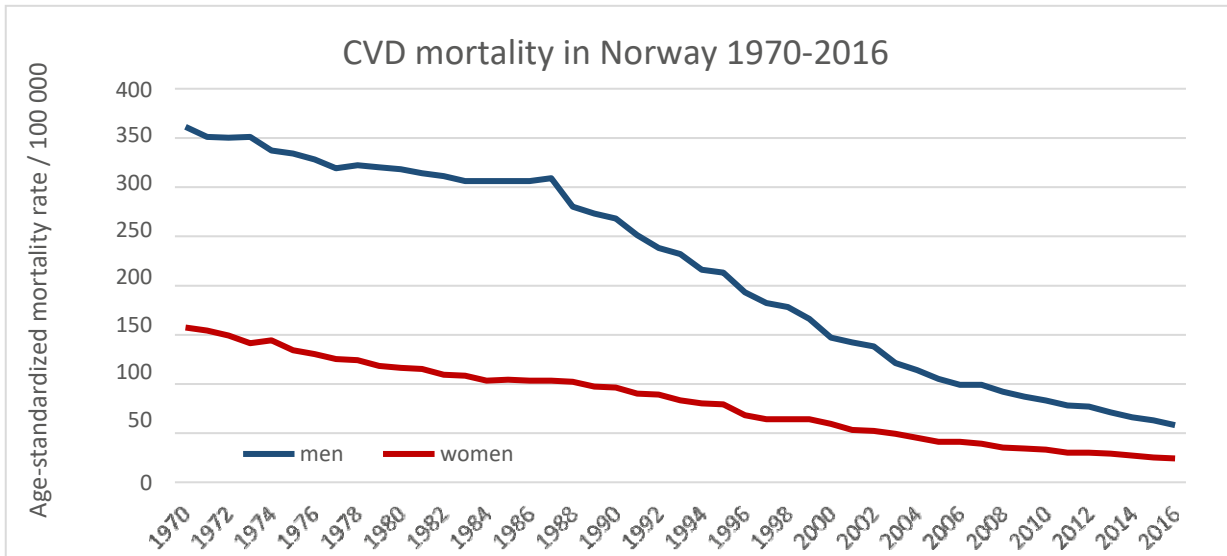
Figure 1: Age-standardized CVD mortality rates in Norway 1970-2015. The rates are standardized using 5-year age groups in the Norwegian population per 1981 as reference. From January 2015 the standard population used is the Norwegian population per 1 January 2012. Source: www.norgeshelsa.no

New Zealand has experienced a similar decline. Figure 2 shows a steady decline in CVD mortality in New Zealand from 1970 until 2013, parallel to the decline in Norway.
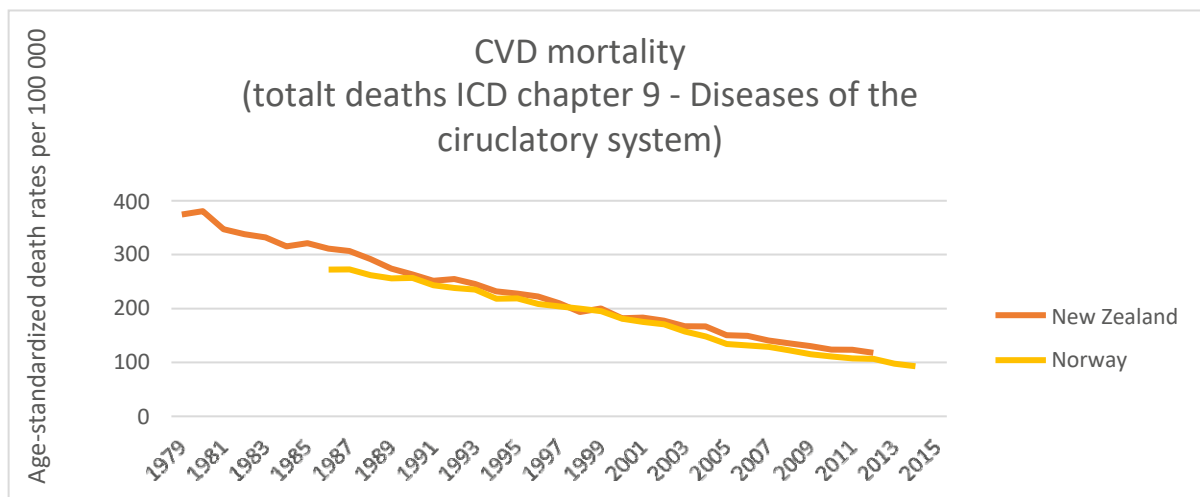
Figure 2: CVD deaths in Norway and New Zealand 1979-2015. Age-standardized using the WHO world standard population. Source: WHO Mortality Database at http://apps.who.int/healthinfo/statistics/mortality/whodpms/

The reasons for the marked decline in CVD mortality in Norway, New Zealand and other high-

income countries could be due to a decline in the incidence/event-rates as a consequence of improved risk factor levels or it could be due to better survival of acute cardiovascular events as a result of better treatment and secondary prevention. The IMPACT model (113) aims to quantify the relative contribution from risk factors or treatment to the reduced CHD mortality. The IMPACT model has not been applied in Norway so far, but it has been used in several other countries including New Zealand (114-120). In the New Zealand study where the IMPACT model was applied, it was found that almost half of the decline in CHD mortality rate in Auckland during 1982-1993 could be attributed to medical therapies, and about another half could be attributed to reductions in major risk factors (114). The WHO MONICA (monitoring trends and determinants in cardiovascular disease) Project has found that in populations where CHD mortality was declining from the 1980's to the 1990's, change in coronary- event rates contributed twice that of trends in case fatality to the change in CHD mortality (121)

Levels in total cholesterol (TC), blood pressure and smoking rates have declined in Norway in recent decades, while the prevalence of overweight and type 2 diabetes have increased (40, 106, 122-124). Although the prevalence of diabetes is increasing, a recent nationwide cohort study showed that the incidence of type 2 diabetes decreased from 2009 to 2014 (125). In a Norwegian study from Tromsø, it was found that during 1995-2010, reductions in the incidence of CHD contributed with 43% and reductions in case fatality contributed with 57% to the decline in CHD mortality (106). Reductions in risk factors during 1994-2008 contributed with together two thirds of the 51% decline in incident CHD during 1995-2010, of which reductions in cholesterol contributed most (32%) (106). These quantifications of the different contributions may not be generalizable to Norway as a whole, but they clearly indicate that the decline in CVD mortality in Norway is due to a combination of improvements in risk factors as well as better treatment and secondary prevention of acute events.

Epidemiologic transition

The shift from nutritional deficiencies and communicable diseases towards chronic non-communicable diseases as the most common causes of death has been described as "the epidemiologic transition" (96, 126, 127). This transition is driven by changes in demographics, economics and social structures (128). Many high-income countries, including Norway and New Zealand, experienced this transition following the industrial and technological advancements of the 19th and 20th centuries. These advancements led to improvements in several public health measures, including nutrition and sanitation (128). Most high-income countries are now in the

fourth stage of the epidemiologic transition where efforts to prevent, diagnose and treat CVDs have managed to delay the onset of these diseases to more advanced stages (126, 128). Some low- and middle income countries are still in earlier stages where infectious diseases are still prominent, but are gradually being replaced by non-communicable diseases as the most common causes of death (126). Limitations to "the epidemiologic transition" theory have been pointed out (100) as not all countries seem go through the stages of the transition that was first described by Omran in 1971 (127). For example, countries in Eastern Europe and Central Asia have experienced a rise in CVD *as well as* in maternal and communicable diseases since 1990. This phenomenon, when some low- and middle- income countries acquire the challenges of later stages of the transition without resolving the challenges of the earlier stages, has been termed "the double-burden" (100).

Moreover, countries might not find themselves in only one phase of the epidemiologic transition. A GBD study recently documented large variations in the epidemiological transition levels across different states in India (102). Also, a recently published nationally representative study in India found large variations within the country regarding the prevalence of diabetes and hypertension and an unexpectedly high prevalence of hypertension among young adults (129). The prevalence of diabetes was higher in urban and Southern states, and variations in the age-standardized prevalence of diabetes ranged from 2.3% [95% CI, 2.0%-2.8%] in women living in Madhya Pradesh to 17.9% [95%CI, 15.4%-20.7%] in men in Goa (129). Although India and China do not have the highest prevalence rates in the world, India and China are the two countries with the highest numbers of people with diabetes (130).

Some regional differences related to CVD mortality
The leading cause of YLL in India in 2016 was coronary heart disease whilst in China it was cerebrovascular disease (93). In East and South-East Asia, several countries (China, Indonesia, Vietnam and South Korea) have twice as many people dying from stroke than from coronary heart disease (100). A high number of stroke deaths is also seen in sub-Saharan Africa. (128). In 2013, estimates from the GBD study found that the risk of dying prematurely due to CVD was highest in Central Asia, followed by Eastern Europe (100).

1.3 Migration and ethnicity in relation to cardiovascular health

1.3.1 Migration

The driving force behind multi-ethnic societies is migration (1, p.92). Migration can be defined as the "movement of people to a new area or country in order to find work or better living conditions" (131). Migration involves change of residence that can be of more or less permanent character. It implies a change in living conditions, which often represents changes in lifestyles with implications (both positive or negative) for health (132). The linkage between health and migration is complex and influenced by a range of factors, such as the migrants' socio-economic and cultural background, the persons' history of health, access to health care (and the quality of this) before moving, circumstances around the migration, as well as the social and health characteristics related to re-settlement in the new country (133). Migration is also considered a health determinant in its own right (134). Some post-migration factors that are important for health are the possibilities to work, general living conditions, access to health care, possibilities to stay in contact with family and friends as well as language skills in the new country (133).

Migration leads to the mixing of populations and has great effects on society for both infectious and non-infectious diseases (1, p. 92-93). Migration can be either forced or voluntary (133) and the drivers are many (135). When discussing ethnic differences in health, mechanisms such as selection, cultural adaptation, and social status differentials may be relevant. These mechanisms are also often related to factors such as reasons for migration, length of stay, age at migration and sending country characteristics (136).

Immigrants may also be exposed to discrimination in the host country, which may affect health in different ways. Discrimination involves systematic unfair treatment and exists in many forms (137). Both Norway and New Zealand do relatively well regarding immigrant's opportunities for taking part in society compared to other countries as measured by the MIPEX indicator (138). However, immigrants in Norway are more often overqualified in their jobs compared with the rest of the population (139), and having a foreign name versus a typical Norwegian name makes it more difficult to get a job (140). Also in New Zealand, a study found indications of discrimination based on the applicant's ethnicity in hiring decisions (141).

Selection mechanisms and the healthy immigrant effect
Lower mortality among immigrants as compared to the host population has been documented in Norway, New Zealand, North America (the US and Canada) and several other countries (136, 142-147). The phenomenon of immigrants having a health advantage compared with the host

populations was at first considered paradoxical since immigrants often tended to have lower socioeconomic status, come from poor countries and have poorer access to healthcare than native-born (145). Explanations for the mortality advantage has been sought and factors like health screening by the authorities in the host country before immigration and lack of data/statistical artefacts as well as selective return-migration of the unhealthy (often referred to as the "salmon bias") have been proposed to influence the observations of lower mortality among immigrants (148). "The healthy migrant hypothesis" or "the healthy immigrant effect" suggests, however, that there are self-selection mechanisms in out-migration; the healthiest choose to (and have the ability to) migrate and so immigrants are often more healthy and resourceful than most people in their countries of origin (148, 149). In Norway, lower mortality was recently found among immigrants coming for work or education purposes, and also among refugees (although refugees had a higher death risk than the work/education-immigrants) (136). The role of the salmon bias as an explanation for the low mortality observations among immigrants has gained limited support (150-153), and studies have also shown some mixed results for the healthy migrant effect (148, 154). However, the healthy migrant effect seems to be most evident and consistent among newly-arrived immigrants in the working age rather than among children, adolescents and the elderly (155, 156). Over some generations, the migrant populations usually converge towards the pattern of disease of the host country (1, p. 93). This was also found in the recent Norwegian study where the mortality advantage in newly arrived immigrants declined with increasing length of stay (136). Such a development could be due to acculturation processes/how the immigrants adapt habits in the new country (which could increase or decrease their risk of disease), environmental exposures in the host country and it could also be related to negative effects of the migration itself.

1.3.2 Ethnicity and cardiovascular disease

Ethnicity is a multidimensional concept and numerous definitions exist. Professor Raj Bhopal defines ethnicity as "The social group a person belongs to, and either identifies with or is identified by others, as a result of a mix of cultural and other factors including one or more of language, diet, religion, ancestry, and physical features (…)" (1, p. 311). The word ethnicity comes from the Greek word ethnos and means nation, people or tribe. This inclusive definition implies that ethnicity is a fluid quality, which may change over time, and consequently, that ethnicity is also an imprecise concept. This means, for example, that Indians in Norway form a different ethnic group than Indians in India or Indians in New Zealand although they do share some common qualities and background.

The Statistics New Zealand has adopted a definition of ethnicity which corresponds to the definition of Bhopal and underlines that ethnicity is self-perceived and that people can belong to more than just one ethnic group (157, 158). Furthermore, ethnicity is regarded a measure of cultural affiliation, and is therefore distinct from race, ancestry, nationality or citizenship (157).

1.3.3 Immigration to Norway

Immigration to Norway accelerated slowly from the late 1960's and gained speed from the 1970's (159). The first wave of immigration from countries outside Europe included unskilled labour migrants coming from Turkey, Pakistan and Morocco. Figure 3 shows the increasing immigrant population since the 1970's by country of birth.
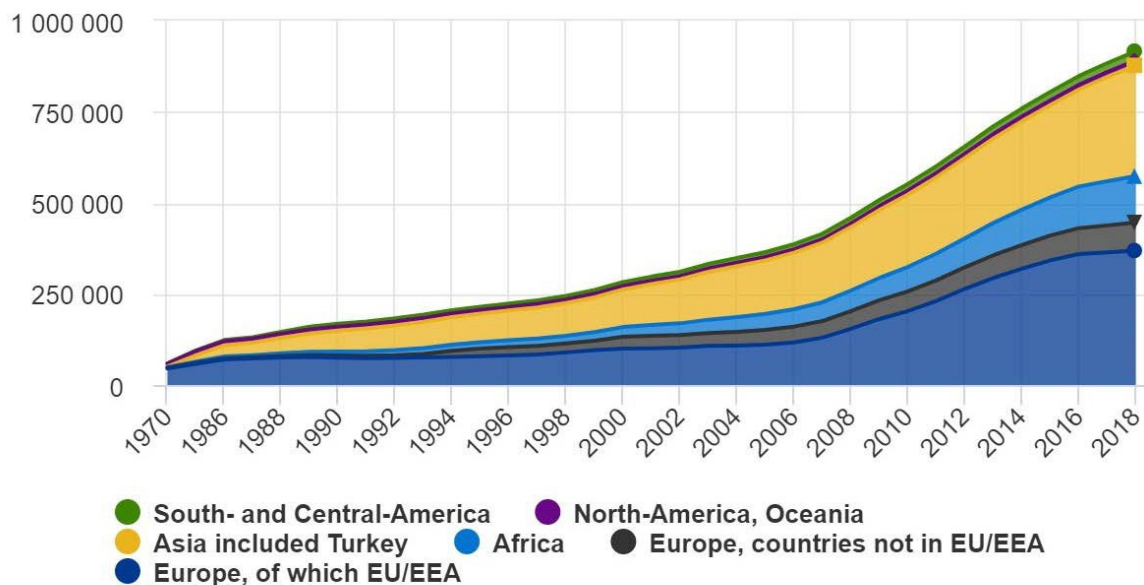
Source: Immigrants and Norwegian-born to immigrant parents, Statistics Norway.

Figure 3. Immigrants and Norwegian-born to immigrant parents, by country background

The share of immigrants in Norway per January 1st 2018 was 14.1 % and Norwegian-born to immigrant parents constituted 3.2 % of the Norwegian population (160). Immigrants in Norway come from 221 different countries and independent states. The total number of immigrants was 746 700 in January 2018 and the ten largest immigrant groups (the latter also including Norwegian-born to immigrant parents) were from Poland, Lithuania, Somalia, Sweden, Pakistan, Iraq, Syria, Germany, Eritrea and the Philippines (160).

1.3.4 Cardiovascular risk among immigrants in Norway

Before the present studies, the incidence of CVD among immigrants in Norway had not been described. The existing knowledge was based on self-reported information about CVD and measurements of risk factors from health surveys such as the Oslo Health Study (including the Oslo Immigrant Health Study) carried out during 2000-2002. A higher proportion of immigrants from low- and middle-income countries has reported about CVD in Norwegian health studies compared with Norwegian-born (161, 162). Higher levels of low HDL cholesterol, increased triglycerides and a higher prevalence of abdominal obesity were found among immigrants from Pakistan and Sri Lanka compared with other ethnic groups in the Oslo Health Study (161, 163). Meanwhile, smoking was very rare (almost non-existent) among women from Pakistan and Sri Lanka. The Oslo Health Studies have also shown that the occurrence of diabetes is very high in immigrants from Pakistan and Sri Lanka (164). In a study carried out as part of my master thesis where we used data from The Cohort of Norway (CONOR – described in section 3.2 and in paper 2), we found that immigrants from the Indian subcontinent had the lowest high-density lipoprotein (HDL) levels, the highest levels of blood glucose, triglycerides, TC/HDL ratio, WHR and self-reported diabetes prevalence among the eleven ethnic groups included in the study (162). This corresponds with information about high risk of diabetes and CVD among immigrants from South Asia from international studies (165) (further elaborated in section 1.3.7). Immigrants from the former Yugoslavia had the highest predicted 10-year Framingham risk score among the eleven ethnic groups (including the Norwegian-born) (162). Immigrants from East Asian countries, on the other hand, had favourable levels of blood lipids, low levels of BMI and waist-to-hip ratio and the lowest Framingham 10-year risk score of all the ethnic groups (162). Most immigrant groups have shown lower levels of systolic blood pressure compared with ethnic Norwegians (161, 162), and immigrants from Vietnam have displayed lower proportions of overweight/obesity measured by BMI and WHR compared with immigrants from Sri Lanka, Pakistan, Iran and Turkey (45, 161).

1.3.5 Immigration to New Zealand

New Zealand has a long immigration history beginning with the first arrival of settlers from Polynesia in the late 13th century (although the timing is somewhat debated) (166). Europeans only became aware that the country existed in 1642 when the Dutch Abel Tasman discovered the land from sea. James Cook, a British explorer, rediscovered New Zealand in 1769 and was the first European to disembark and explore the country. Cook was also the first to draw the full outline of New Zealand on his first journey in 1769-1770, placing New Zealand on the world map (166). New Zealand was annexed the British Empire as part of the Colony of New South Wales in 1840 (166),

which marked the time when the Europeans began to arrive New Zealand with planned settlements. Since then, New Zealand has had many waves of immigration particularly from the Great Britain, France, China, the Netherlands, the Pacific Islands and later from other Asian countries including India (167). Today, New Zealand is one of the OECD countries with the highest foreign-born populations, constituting 22.4% in 2013 (168).

The latest available census information from New Zealand is from 2013 and showed that the largest ethnic groups were European (74%), Máori (15%), Asian (12%) and Pacific peoples (7%)[3] (169). Within the Asian group, Chinese constituted the largest ethnic group and Indians the second-largest (170). The Indian ethnic group grew faster than the Chinese ethnic group between the censuses in 2001 and 2006 and also between the censuses in 2006 and 2013 (170).

Indians (including Fijian Indians) represented about 4% of those who stated an ethnic group in the New Zealand population in 2013, counting 155 178 individuals (171). The number of migrants from India to New Zealand has increased in recent years (172), and the number of Indian-born residents more than doubled from 2001 to 2006. In 2013, approximately 56% of the Indian ethnic group were born in India which counted 65 157 individuals (171, 172).

1.3.6 Cardiovascular risk among South Asians in New Zealand

As described in paper 2 and 3, it is only possible to identify ethnic Indians among the South Asian ethnic group in New Zealand health statistics. Other South Asians, such as Pakistanis, Bangladeshis and Sri Lankans are all part of the "Other Asian" group in New Zealand national health data. The available information on health among South Asians in New Zealand is therefore mostly represented by the Indian ethnic group. A high risk of CVD in Indians compared with the total New Zealand population, Chinese and Other Asian ethnic groups has been found in New Zealand hospital data (173). This increased risk was especially marked in Indian males and in particular for CHD. In the youngest group, 25-44 years, Indian males had more than triple the risk of CHD hospitalisations when compared with the total New Zealand population (173). Indians in New Zealand also have an increased risk of stroke compared with the total New Zealand population, but not as marked as for CHD (173). A previous study, based on data from the PREDICT cohort, showed that Indians had a two- to four-fold higher burden of diabetes (50% of the Indians aged 65-74 had diabetes), lower blood pressure measurements, lower smoking rates and that they more often live in deprived areas in New Zealand when compared to Europeans (174). No clinically significant

---

[3] These percentages represent the proportions of people who identified with at least one of the ethnic groups and do not add up to 100%.

differences in mean TC/HDL ratios were found between Indians and Europeans (174).

1.3.7 High risk of CVD in South Asian populations

The South Asian region is the most populated region in Asia constituting nearly a quarter of the world's population (when India, Pakistan, Bangladesh, Iran, Afghanistan, Nepal, Sri Lanka, Bhutan and Maldives are all included) (175). A large number of South Asians also live outside the Indian subcontinent with estimates of about 3 million South Asians in the UK, 1.6 million in Canada, 1.3 million in South Africa, 3 million in the US, and relatively large populations in many other European countries, the Middle East, Australia, and several African countries (176). South Asian populations have been found to have a high risk of CVD, particularly CHD, in several countries when compared to their host populations and other ethnic groups (177-181). The first report of higher CHD rates in South Asians compared with other ethnic groups came from a study in Singapore based on autopsies, comparing the results from post-mortem examinations in Chinese and Indian subjects, carried out during 1950-1954 (182). Similar discoveries of higher CHD mortality rates in South Asians were later made in the UK in the 1970's and 1980's (183, 184). A high risk of CVD in South Asian populations is now well documented in the UK (12, 18, 185, 186) as well as in several other Western European countries (179, 187, 188), and in New Zealand (173) as mentioned in the above section. South Asians, especially when living in high-income countries, also have an increased risk of type 2 diabetes compared to Europeans, and South Asians develop diabetes at a younger age than their European counterparts (189). Studies have also shown that South Asians develop CVD earlier than Europeans. For example, the large INTERHEART study found that the median age at first myocardial infarction was 53 years in South Asia and 59 years for other regions of the world (190). It is likely that the increased risk of diabetes in South Asians plays an important role for the increased risk of CVD in this ethnic group. In the Indian subcontinent, there is also a high and increasing burden of CVD (191, 192). In 2005 it was stated that India is the country in the world with the highest loss of potentially productive years of life due to CVD deaths in the age group 35-64 years (192).

Different hypothesis have been proposed to offer explanations for the high risk of CVD in South Asian populations. Among these is the foetal origins hypothesis or the thrifty phenotype hypothesis which underlines the significance of early life environmental exposures for the risk of later disease, and propose that undernutrition in utero/early life may contribute to a predisposition to type 2 diabetes, obesity, high blood pressure and cardiovascular disease in adult life (193-195). This hypothesis is also known as the "Barker" hypothesis as it was introduced by Hales and Barker in

21

1992 (194) and arose from studies led by David Barker (196). Meanwhile, in Norway, many know this hypothesis as the "Forsdahl-Barker hypothesis" due to the early discoveries by Anders Forsdahl of associations between living conditions in early life and mortality from arteriosclerotic heart disease in adult life (197). Support for the explanatory role of this hypothesis for the increased risk of CVD in South Asians has been found in studies demonstrating a lower birth weight in South Asians compared to Europeans and more adipose tissue (the "thin-fat" phenotype) (198-202). Some of the studies also found higher levels of insulin in the cord blood when they adjusted for birth weight (202, 203). A number of additional hypotheses have been set out to offer possible explanations for the mechanisms behind the high risk of CVD and metabolic risk factors in South Asians. These will not be elaborated here, but some examples are; the adipose tissue overflow hypothesis (204), the El niño hypothesis (205), the high-heat food preparation hypothesis (206), the mitochondrial efficiency hypothesis (207) and a behavioural switch hypothesis (208). Another study found that South Asians had less brown adipose tissue (209) and associated lower resting energy expenditure than Dutch Europeans, and therefore suggested that this was an underlying mechanism for the adverse metabolic profile in South Asians (210). In addition, there is a range of novel risk factors that may contribute to the high risk of CVD in South Asian populations (211, 212). Some novel risk factors that have been found to be higher in South Asians than other ethnic groups are: fibrinogen, homocysteine, lipoprotein (a), and plasminogen activator inhibitor-1 (211). It has been proposed that South Asians do not only have lower HDL levels, but that they also have more dysfunctional and pro- oxidant HDL than other ethnic groups (213). The increased risk of CVD in South Asians is not fully understood and researchers are actively searching for explanations.

2.0 Rationale and aims

The rationale for this study was lack of information about the incidence and mortality from CVD among immigrants in Norway. Furthermore, we are only aware of two studies (both conducted in the UK) prior to the initiation of this study that have examined the prospective relationship between established risk factors and later CVD in South Asians, although some additional studies have emerged during our work with this project. As far as we are aware, only one published study has reported statistical measures (discrimination and calibration) for the external validation of existing risk prediction models among South Asians. Furthermore, the role of obesity and socioeconomic factors in addition to the other risk factors in South Asians and Europeans is unclear. This project had four aims:

1. To describe the burden of CVD among immigrant groups living in Norway.
2. To prospectively study the relationship between conventional risk factors and later CVD in South Asians compared with Europeans in Norway and New Zealand, and to study to what extent the risk factors could explain any possible differences in the risk of first CVD events between the ethnic groups.
3. To examine the validity of the Framingham risk score for predicting risk of CVD in South Asians compared with Europeans.
4. To assess the additional role of obesity and social deprivation on the risk of CVD in South Asians compared with Europeans.

3.0 Materials and methods

Detailed methods are described in each of the papers. For the sake of completeness, I give a brief overview here. All the papers had a prospective study design.

3.1 Data sources in paper 1

The Cardiovascular Disease in Norway (CVDNOR) project

In paper 1, we used data from the CVDNOR project which is a collaborative research project between the Norwegian Institute of Public Health (formerly the Norwegian Knowledge Centre for the Health Services) and the University of Bergen (214). Details on CVDNOR are given in paper 1 and elsewhere (215). In short, CVDNOR provided information about all hospital stays related to CVD in Norway during 1994-2009. The hospital data were extracted from the patient administrative systems in all Norwegian somatic hospitals and were further linked with other data sources, such as

the Person Registry in Norway, The Causes of Death Registry and sociodemographic data from Statistics Norway.

This linkage gave us a unique possibility to study the risk of AMI and stroke for the whole Norwegian population over a 16-year period stratified by country of birth. CVDNOR was also used for the endpoints in the Norwegian data in paper 2.

3.2 Data sources in paper 2 and paper 3

In paper 2, we used data from two different cohorts – one New Zealand cohort (PREDICT) and one Norwegian cohort (CONOR). In paper 3 we, used an updated version of the New Zealand (PREDICT) cohort from paper 2.

The PREDICT cohort

The PREDICT cohort is described in paper 2, paper 3 and elsewhere (216). Briefly, the PREDICT cohort contains data on individuals undergoing risk assessments in New Zealand primary care using a web- based decision support software called PREDICT. The PREDICT software was first implemented in Auckland in 2002. About 35-40% of general practices in New Zealand now utilize this software. In paper 2 we used PREDICT data from August 2002 to September 2012, and in paper 3 we used PREDICT data from August 2002 to October 2015 (with follow-up on endpoints until December 2015). In both papers, we used risk factor information on European and Indian individuals. The PREDICT cohort is an open cohort which means that the cohort members were recruited continuously throughout the study period. The cardiovascular risk profiles were linked with national health databases including all public hospitalisations, mortality statistics, publicly-funded drug dispensing and regional laboratory test results (216). Information about risk factors and outcomes is given in the respective papers. The PREDICT templates that were introduced in 2004 are attached to this thesis in appendix 1.

The cohort of Norway

The Cohort of Norway (CONOR) is a collection of several Norwegian health surveys carried out during 1994-2003 (217). In paper 2, we used data from the three CONOR surveys with the majority of the immigrants, conducted in Oslo in 2000-2002; The Oslo Health Study (HUBRO), The Oslo Immigrant Health Study (I-HUBRO) and The Romsås in Motion study (MoRo II). CONOR contains information on health variables collected through self-administered questionnaires (the

questionnaire is attached to this thesis in appendix 2), physical measurements and blood samples. All the CONOR surveys followed the same standard procedure for data collection. The CONOR data were linked with hospitalisations and deaths in the CVDNOR-project providing follow-up information on cardiovascular endpoints until 2009 (215). The risk factors in CONOR and outcomes in the CONOR- CVDNOR linkage has been described in the paper.

3.4 Study populations

3.4.1 Paper 1

In paper 1, we studied the whole Norwegian population aged 35-64 years during 1994-2009 (n=2 637 057). Figure 4 provides an overview of the study population in paper 1.

CVDNOR

The whole Norwegian population 1994-2009, n= 7 905 304

Excluded:
- Outside age-range 35-64, *n*=5 253 181
- No information on country of birth, *n*=1 310
- Foreign-born with both Norwegian-born parents, n=13 746
- Birth countries: St. Helena (*n*=5), the British Indian Ocean Territory (*n*=1), the Maldives (*n*=2) and the Falkland Islands (*n*=2)

Study sample (*Population at risk*):
The whole Norwegian population,
Aged 35-64, 1994-2009

n= 2 637 057 (49% women) of which n=282 485 immigrants (11%)

Identification of AMI events (linkage with hospital data)

Excluded:
-Individuals with more than 3 events before aged 35, n=1
- Recurrent AMI events ≥4, n= 295 (17% women)

Identification of stroke events (linkage with hospital data)

Excluded:
- Rehabilitation as main diagnosis (stroke secondary), n=?
-Individuals with more than 3 events before aged 35, n=10

Individuals with a stroke hospitalization and/or stroke death *n*=34 392 (37% women)
- No of total events (≤3 per person): 43 252

- No of hospitalized events: 42 073
- No of deaths outside hospital: 1 179

Individuals with an AMI hospitalization and/or AMI death *n*=59 314 (20% women)
- No of total events (≤3 per person): 67 683

- No of hospitalized events: 61 301
- No of deaths outside hospital: 6 382

Figure 4: Inclusion flow chart for the study population in paper 1.

26

3.4.2. Paper 2

In paper 2, the study population consisted of South Asians and Europeans aged 30-74 years without a history of CVD in a New Zealand (n=129 449) and a Norwegian cohort (n=16 606). Figure 5 depicts the study population from the New Zealand cohort and Figure 6 depicts the study population from the Norwegian cohort.

The PREDICT cohort
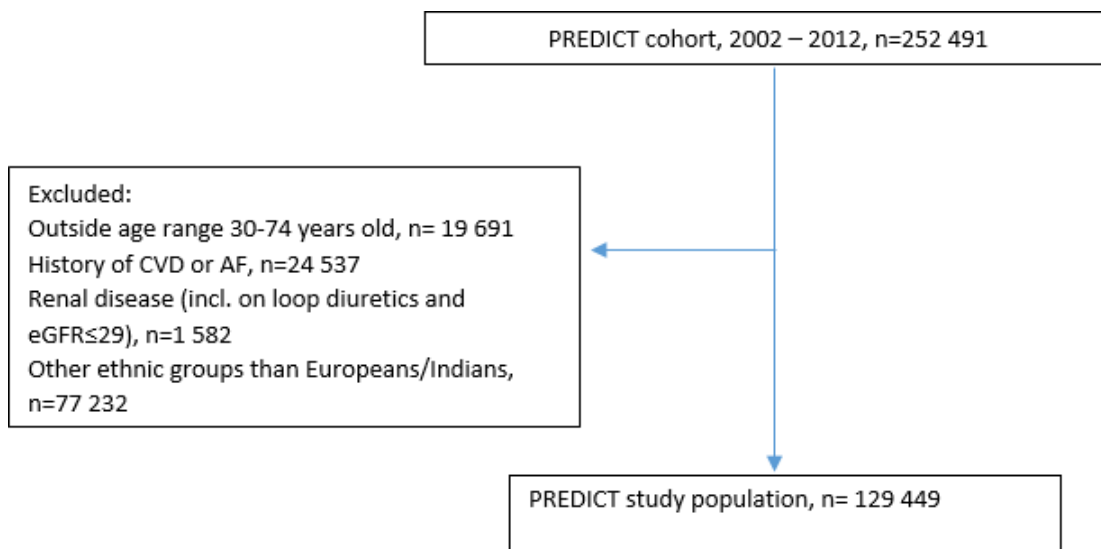
Figure 5: Flow chart for the study population in the New Zealand dataset in paper 2, the PREDICT cohort.

The Cohort of Norway (CONOR) linked with CVDNOR


```
┌─────────────────────────┐        ┌──────────────────────────────────────┐
│ CONOR, total participants│───────▶│ CONOR, total individuals               │
│ n= 180 553               │        │ (Restricted to first time attending a   │
│                          │        │ CONOR-survey)                          │
└─────────────────────────┘        │ n=173 243                              │
            │                        └──────────────────────────────────────┘
            ▼                                          │
┌────────────────────────────────┐                    │
│ Excluded:                       │                    │
│ Duplicate participant data, n= 7310 │                │
└────────────────────────────────┘                    │
                                                       ▼
┌──────────────────────────────────────────────────┐
│ Excluded:                                          │
│ - Participants from other CONOR surveys, n=146 434 │◀───┐
│ - Participants from intervention studies (HYRIM/DOIT/LIFE), n=100 │
└──────────────────────────────────────────────────┘
```

Health surveys conducted in Oslo (HUBRO, I-HUBRO and MoRo),
n=26 709

Excluded:
- Outside age range, n=3 871
- Missing on country of birth, n=1 309
- Not born in Norway or South Asia, n= 4 342
- Pregnant women, n=197
- Previous CVD (CHD/CEREBRO/ASVD/TIA/HF) based on hospital data, n=353
- Previous AF, n=31

Main sample: participants of Oslo health surveys aged 30-74 at baseline, n=16 606

Figure 6: Flow chart for the study population in the Norwegian dataset in paper 2 (the Cohort of Norway)

3.4.3 Paper 3

The study population in paper 3 consisted of Indians and Europeans aged 30-74 years without prior CVD at the baseline examination (n=256 446). The flow chart for the study population in paper 3 is included in the paper (Figure 1) and is not reproduced here. The update of the PREDICT cohort from paper 2 to paper 3 involved almost a doubling of the number of participants and an increase in the mean follow-up from 2.9 years in paper 2 to 4.2 years in paper 3.

3.5 Statistical methods

The statistical methods are described in detail in the papers. Briefly, statistical analyses were performed using STATA versions 11, 13 and 14. In paper 1, the direct standardization method was used to estimate age-standardized AMI and stroke event rates for immigrants and ethnic Norwegians, and Poisson regression was used to calculate rate ratios with ethnic Norwegians as reference group. In paper 2, Cox regression was used to study the prospective relationships between the major risk factors (SBP, TC/HDL ratio, diabetes and smoking) and subsequent CVD, and to study the contribution from the conventional risk factors to the excess risk of CVD in South Asians versus Europeans. We again used Cox regression in paper 3 to study the prospective relationships between BMI and deprivation and subsequent risk of CVD with and without adjustment for the Framingham risk score. Discrimination of the Framingham 5-year risk score was measured by the area under the receiver operating characteristics (ROC) curve (AUC) and calculation of Harrell's C. Calibration was measured graphically in a plot of predicted minus observed event rates (calculated by the life table method) within deciles of predicted risk.

Some additional information about the statistical methods is given below.

Mediation analyses in paper 2 (main analyses presented in Table 3 in the paper)

To estimate how much the excess risk of CVD in South Asians was mediated through the four major risk factors, we calculated the percentage of excess risk mediated (PERM) according to the formula below as adapted and described by The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI mediated effects) in 2014 (31).

$$PERM = \frac{HR_{\text{(confounder adjusted)}} - HR_{\text{(confounder and mediator adjusted)}}}{HR_{\text{(confounder adjusted)}} - 1} *100$$

Confounder adjusted in our analyses meant adjusting for age and mediator adjusted involved adjustment for the four major risk factors.

Supplementary sensitivity analyses in paper 3 (see sections 4.1.4 and 5.2.3)

While working with paper 3, I performed some sensitivity analyses that were not mentioned in the paper to examine the possible effect of medication use on the overestimation of risk in Europeans and in Indian women. I repeated the calibration analyses after resetting the risk factor values for those who were dispensed medication during follow-up according to treatment goals. This meant that for the calculation of predicted risk, I reset SBP to maximum 140 for those who were dispensed

with antihypertensive medications during follow-up and TC/HDL ratio to maximum 4.5 for those who were dispensed with lipid lowering medications during follow-up, and maximum predicted risk were set to 15% if dispensed either of the two. See figure 7 in 4.1.4.

3.6 Ethical considerations

The project was approved by the Regional Committee for Medical Research Ethics, Health Region West. The project was first approved as a sub-project to the CVDNOR-project. The Regional Committee for Medical Research Ethics changed their procedures during the project period, and we therefore had to apply for an approval that was specific to this project. Such an approval was granted in the end of 2015. The approval also included the use of New Zealand data given that New Zealand regulations were followed.

The PREDICT study was approved by the Northern Region Ethics Committee Y in 2003 (AKY/03/12/134), and since 2007 it was approved annually by the National Multi Region Ethics Committee (MEC07/19/EXP).

4.0 Results

4.1 Synopsis of the papers

4.1.2 Paper 1

Ethnic inequalities in acute myocardial infarction and stroke rates in Norway 1994-2009: a nationwide cohort study (CVDNOR)

In this nationwide cohort study, 59 314 individuals experienced at least one AMI event (in which a total of 67 683 AMI events were observed when up to 3 events per person were included) and 34 392 individuals experienced at least one stroke event (with a total of 43 252 stroke events when up to 3 events per person were included) during 1994-2009. The study revealed large variations in both absolute and relative risks of AMI and stroke between ethnic groups living in Norway. Immigrant men and women from South Asia had more than double the risk of AMI compared with Norwegian-born men (rate ratio (RR), 2.27 [95% CI, 2.08-2.49]) and women (RR, 2.10 [95% CI, 1.76-2.51]). Immigrant men from the Former Yugoslavia and the Middle East had around 50% increased risk compared to Norwegian-born men, and immigrant women from the Former Yugoslavia had 75% increased risk compared to Norwegian-born women. The lowest risk of AMI was seen in

immigrants from East Asia with a RR of 0.38 in both men [95%, 0.25-0.58] and women [95%, 0.18-0.79]. The only ethnic group with increased risk in both genders when compared with Norwegian-born in regard to stroke was immigrants from South Asia. Men from Former Yugoslavia and men from Sub-Saharan Africa also had a higher risk of stroke compared with Norwegian-born (RR, 1.28 [95% CI, 1.09-1.49] and RR, 1.44 [95% CI, 1.20-1.74] respectively), but the women from these countries did not. Reduced risk of stroke was found in immigrant men from North Africa (RR, 0.59 [95% CI, 0.40-0.86]), North America (RR, 0.64 [95% CI, 0.46-0.87]) and Eastern Europe (RR, 0.78 [95% CI, 0.63-0.97]).

4.1.3 Paper 2

Can traditional risk factors explain the higher risk of cardiovascular disease in South Asians compared to Europeans in Norway and New Zealand? Two cohort studies

In this binational prospective cohort study, we used data from a New Zealand (=129 449) and a Norwegian cohort (n=16 606). Participants in the New Zealand cohort were older than in the Norwegian cohort, and Indians were 6-8 years younger than Europeans in the New Zealand cohort. In both cohorts, South Asians had higher TC/HDL ratio and more diabetes at baseline than Europeans, but lower blood pressure and smoking levels. After adjustment for age, the major risk factors (SBP, TC/HDL ratio, diabetes and smoking) were positively associated with subsequent CVD in both ethnic groups, in both genders and in both countries. South Asians had increased risk of CVD compared with Europeans in both countries with age-adjusted hazard ratios (HRs) ranging from 1.42 to 1.92. After adjusting for all major risk factors, the HRs for excess risk of CVD in South Asians versus Europeans were 1.64 [95% CI, 1.43-1.88] in men and 1.39 [95% CI, 1.11-1.73] in women in the New Zealand cohort. Corresponding HRs were 1.57 [95% CI, 1.19-2.07] in men and 1.76 [95% CI, 1.09-2.82] in women in the Norwegian cohort.

4.1.4 Paper 3

Performance of a Framingham cardiovascular risk model among Indians and Europeans in New Zealand and the role of body mass index and social deprivation

During the study period between August 2002 and December 2015, the PREDICT CVD-cohort members were followed for a mean of 4.2 years. Among the 222 083 Europeans (43% women) and 34 383 Indians (41% women), we observed a number of 8105 and 1156 CVD events in Europeans and Indians respectively. Again, we found that Indians had higher TC/HDL ratios and a higher

diabetes prevalence (more than threefold) than Europeans, but lower smoking and SBP levels. Indian men had lower mean levels of BMI and were less overweight or obese compared with European men, while Indian and European women had similar BMI levels. About 50% of the Indians lived in the two most deprived area quintiles in New Zealand while for Europeans the corresponding share was 25%. The observed 5-year event rates were lower than the predicted rates in all groups except in Indian men where the observed and predicted event rates were the same. The Framingham 5-year risk score discriminated better in Indians than in Europeans with AUCs of 0.76 in Indian men and women versus 0.74 and 0.72 in European men and women respectively. The calibration plot showed that the Framingham risk score overestimated the risk in higher deciles of predicted risk, and more so in Europeans than in Indians. The calibration also showed that the best correspondence between predicted and observed risk was seen in Indian men. Both BMI and deprivation were positively associated with CVD in both ethnic groups, also after adjustment for the Framingham risk score.

The additional sensitivity analyses (not presented in the paper) where we reset the risk factor values for those who were dispensed with antihypertensive and/or lipid lowering medication during follow- up did not result in any substantial changes in calibration. See figure 7.
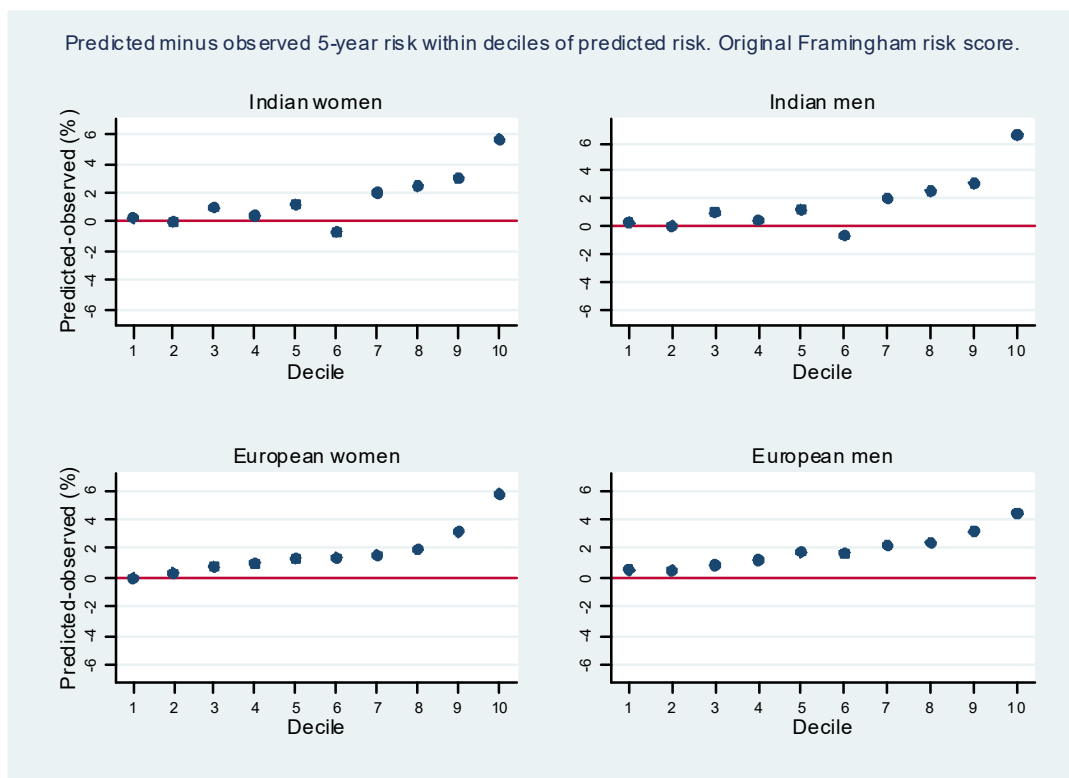

Figure 7. Sensitivity analyses resetting SBP, TC/HDL ratio and predicted risk according to treatment goals if dispensed with preventive medication during follow-up. Note that the x-axis represents the deciles of predicted risk, not predicted risk values as in the main calibration analyses in paper 3.

5.0 Discussion

5.1 Methodological considerations

5.1.1 Validity

Validity is usually divided into internal and external validity (218). Internal validity refers to the validity of inferences drawn for the members of the source population, while external validity refers to the validity of inferences drawn for persons outside that population (generalizability). Internal validity is a prerequisite for external validity (218).

Study design

As all three papers had a prospective study design, they share the strength of having collected the information about exposure prior to the outcome, minimising the possibility that the disease could have influenced the exposure information (218).

The study design in paper 1 was a nationwide cohort study including all Norwegian residents with information about CVD endpoints from hospital data linked with information from registry data. Problems with selection bias, loss to follow-up and generalizability were therefore reduced. However, there are some limitations using registry data in health research which are often related to data being collected by others than the researcher and for other purposes (219). Some limitations that could be relevant for our study are that registry data may lack important information (for example, if persons who emigrated did not report their moving to the Norwegian Tax Administration) and that the quality of data might be hard to evaluate in lack of a "gold standard" (219). We cannot rule out the possibility of unregistered emigrations, but do not expect this to be a large problem. The quality of data relating to the validity of cardiovascular endpoints is discussed later in this section under the sub-headings "information bias" and "misclassification of endpoints".

A strength of paper 2 was the inclusion of two separate cohorts with consistent results. As there is a great lack of cohort studies reporting the prospective relationships between risk factors and subsequent CVD in South Asian populations, the binational prospective study design of paper 2 is a strength. Paper 3 shares the strength of paper 2 in filling a gap of prospective cohort studies reporting the relationships between risk factors and subsequent CVD in South Asians, as well as the validation of a well-known cardiovascular risk prediction score in a high risk ethnic group where its validity has been largely unknown.

Internal validity

Selection bias

Selection bias can occur if the effect estimate is distorted by factors that influence participation or selection into a study (218).

As mentioned, selection bias was not very relevant for paper 1 as we studied the whole population in Norway. Also, since Norway is a country with universal health care, since we studied acute conditions and since deaths outside hospital were included, it is not very likely that differential use of health care services between the ethnic groups could have distorted our findings. Furthermore, we updated the population at risk every year so that only persons who were registered as Norwegian residents and alive contributed with person-years to the denominator.

Potential selection bias due to self-selection into the Norwegian cohort in paper 2 cannot be ruled out. We used risk factor information from three Oslo Health Studies in CONOR with participation rates ranging from 40-46% (217). One of the included Oslo surveys (the Oslo Immigrant Health Study), had a final overall response rate of 40%, and participation rates for those born in Sri Lanka and Pakistan were 51% and 32% respectively (163). It is not uncommon that participants in population-based cohort studies are healthier and have higher socioeconomic positions than non-participants (220-222). A validation study from the Oslo Health Study found that men, young, single, people born outside Norway, residents in inner cities, persons with lower levels of education and lower income as well as those receiving disability benefit were underrepresented (223). Due to a larger underrepresentation of disability benefit receivers in the Norwegian-born group than in the non-western immigrant group, the validation study found a slight overestimation of the odds ratio for disability benefit in non-western born compared to Norwegian born when calculated from attendees only (223). Similarly, there could be a possibility of some selection bias affecting the comparisons of CVD between the ethnic groups in paper 2 if the Norwegian-born group in the Oslo Healthy Study are in fact more selectively healthy (which could involve being more health conscious during follow-up) than the non-western immigrant group. However, since we adjusted for the major risk factors, any relevant health difference between the groups would be limited in the full-adjusted model in paper 2. It is also reassuring that the ethnic comparisons in paper 2 demonstrating a high risk of CVD (and a particularly high risk of CHD) in South Asians versus Norwegian-born, correspond to the results in paper 1 where self-selection was not a problem. The RRs for the risk of AMI in South Asians versus Europeans in paper 1 were 2.27 [95% CI 2.08 to 2.49] in men and 2.10 [95% CI 1.76 to 2.51] in women. In paper 2, the corresponding age-adjusted HRs for CHD were 2.45 [95% CI 1.82 to 3.30] in men and 3.23 [1.95 to 5.34] in women (these estimates from paper 2 can be found

in the online supplementary material, table A9).

For the New Zealand data in paper 2 and 3, the participants consisted of persons undergoing risk assessments in the primary care, which implies that individuals with high levels of risk factors were over-represented in the cohort compared with the New Zealand general population. New Zealand guidelines recommend that men aged 45-75 years and women aged 55-75 years should be risk assessed every 5 years regardless of risk factors. Certain high-risk groups, including people from the Indian subcontinent and people with known cardiovascular risk factors are recommended to undergo risk assessment 10 years earlier (224). Indians are therefore also over-represented in the PREDICT cohort (216). This means that findings from the PREDICT cohort is not generalizable to the New Zealand general population, but the cohort is representative for those who are eligible for risk assessment according to the New Zealand guidelines. Since asymptomatic people in certain age-groups are recommended to undergo risk assessment, and because around 90% of all New Zealanders meeting the eligibility criteria underwent risk assessment between 2010 and 2015 as a result of a nationally coordinated and funded programme (225), the PREDICT cohort should be generalizable to large parts of the New Zealand population (men aged 45-74 years and women aged 55-75 years). The representativeness of the PREDICT cohort is increasing, which means that it was higher in paper 3 where follow-up lasted until 2015 (over 90% of all eligible individuals in the primary health organizations where PREDICT is used had been risk assessed by 2015 (225)) than in paper 2 where follow-up lasted until 2012 (between 79-88% of the eligible individuals in the primary health organizations using PREDICT had been risk assessed by 2012 (216)). Around a third of the New Zealand population belong to clinics where the PREDICT software is used, which is mainly in the Auckland and Northland regions – two regions representing large urban and rural areas with diverse socioeconomic and ethnic populations (226). We cannot rule out the possibility that some recruitment bias might have affected the ethnic comparisons, as discussed above for the Norwegian cohort. Indians were about 6-8 years younger than Europeans in both paper 2 and 3, reflecting the New Zealand guideline recommendations. Adjusting for age was therefore particularly important in order to control for confounding due to the selective recruitment of young Indians into the cohort. While working with paper 3, we also discovered that younger participants had high levels of risk factors (results not shown), and we therefore did sensitivity analyses to check whether it could have affected the results. This involved repeating the calibration analyses without men <45 years and women <55 years (the cut-offs for when risk assessment is recommended for the asymptomatic general New Zealand population without any known risk factors), which gave similar results as the original analyses (not shown).

For the purpose of validating a cardiovascular risk prediction model in paper 3, the PREDICT cohort population was appropriate as it represented the setting in which risk prediction models are intended. Selection bias is, thus, not very relevant for paper 3.

The extent of missing information was small (only 0.01% for the New Zealand PREDICT data and 3% for the risk factor with most missing in the Norwegian data in paper 2). It is therefore not likely that this has had any essential effect on the estimates.

Loss to follow-up in paper 2 and 3 was negligible due to the use of hospital data in two countries where hospital treatment is free of charge and also by including deaths outside hospital from mortality registries. In the New Zealand data, the only ones who would not be captured in the national hospital and mortality registries in addition to people travelling abroad or those who emigrated during follow-up were participants treated in private hospitals (216). Private hospitals represent less than 2% of all hospital admissions related to cardiovascular disease in New Zealand (226), and furthermore, most of the private hospital admissions are for non-acute procedures (110). We have no information about emigrations in the New Zealand cohort, but for the Norwegian cohort in paper 2 we know that few emigrated (around 1% of ethnic Norwegians and <3% South Asians in the Oslo health studies had emigrated during follow-up).

For paper 2 and 3 we excluded people with previous CVD. This could potentially create some selection bias if the exclusions were more or less correct for the different ethnic groups. In the Norwegian data in paper 2, we used hospital data to exclude persons with prior CVD. It is possible that South Asians to a larger extent than ethnic Norwegians could have had unregistered CVD hospitalisations if they, for instance, experienced a CVD event before migrating to Norway or while visiting their countries of origin. Norwegians could also have experienced CVD events while staying abroad. After we excluded people with prior CVD hospitalisations, about 1% of the South Asians reported to have ever had a stroke or a heart attack in the CONOR questionnaire, while for the ethnic Norwegian group this percentage was < 0.5 for both outcomes. The reason we excluded solely based on hospital data and not based on self-reported events was that we were uncertain about the validity of the self-reported disease events and whether the validity could differ between the ethnic groups, more so than the validity of the hospital data. We also excluded persons with previous CVD events in the New Zealand cohort. A recent New Zealand study has examined the accuracy of general practice registrations of prior CVD identified at the time of CVD risk assessments, and found that it was more likely for people <55 years, women, Māori, Pacific, Indian and Asian ethnic groups to have prior CVD inaccurately recorded (227). Smokers and people with diabetes were more likely to have prior CVD correctly identified, and as much as 39% of people with

prior CVD hospitalisations were wrongly registered as having no history of CVD. Thus, we cannot rule out the possibility that some systematic differences exist between the ethnic groups regarding their history of CVD.

Information bias (misclassification)

Information bias refers to errors in the collected information from the study subjects. For discrete variables, this is called misclassification (218). The key variables to consider regarding misclassification are exposure and disease (228).

When misclassification depends on the actual values of other variables it is called differential misclassification (218). This kind of misclassification can either exaggerate or underestimate an effect. Non-differential misclassification, on the other hand, occurs when misclassification does not depend on the actual values of other variables. Bias introduced by non-differential misclassification usually distorts the effect towards the null, although there are exceptions to this "rule" (218).

Misclassification of ethnic groups

For the Norwegian data in papers 1 and 2, we used country of birth as an indicator of ethnicity. The main disadvantage with country of birth for this purpose is that people who are born in the same country might have different ethnic backgrounds (229, 230). The possibility that some subjects have been misclassified on ethnicity cannot be ruled out, but such misclassification is probably independent on the values of other variables and would therefore be non-differential. The main consequence of such misclassification would be that our findings would not be equally applicable to all ethnic subgroups within the group. The high risk of AMI and stroke among South Asian women in paper 1 seemed to be mostly driven by a high risk among women born in Pakistan and not as much by the women who were born in Sri Lanka and India (see Tables 1 and 2 in paper 1). It is worth to note, however, that Pakistan was the best represented country of birth within the South Asia group and that the uncertainty measures for the estimates for Sri Lankans and Indians were large. Due to the heterogeneity in large ethnic categorisations, it is a strength that we had the possibility to present estimates for single countries of birth (although country of birth is also a crude ethnicity measure) in addition to the larger regions of birth in paper 1. This was, unfortunately, not possible for the Norwegian data in paper 2 due to privacy protections. Advantages using country of birth to indicate ethnicity are its objective and stable qualities making it possible to compare between studies and over time (although this should be done with caution due to the fluid and dynamic nature of ethnicity) (229, 230).

Ethnicity in the New Zealand data in paper 2 and 3 was based on self-identification coded according to pre-defined categories. This ethnicity information came from the National Health Index dataset and the PREDICT template. In correspondence with the understanding of ethnicity held by Statistics New Zealand, the members of the cohort can enter up to three different ethnicities. As described in paper 2 and 3, a prioritising algorithm is used in case of multiple ethnicities recorded (see online supplementary file in paper 2 entitled the VIEW Ethnicity Protocol). Self-identification of ethnicity is a more precise measure of a persons' ethnicity (in the view of ethnicity being fundamentally self-perceived), but less consistent and comparable than country of birth, and, moreover, it is not subject to control of the investigator. Thus, it is not a perfectly suitable measure for research (230). The prioritisation aims at assigning people to a single ethnic group while preserving consistency in the New Zealand statistics, and avoid that small groups get absorbed by the New Zealand European ethnic group. The prioritisation procedure has some downsides, however, as some groups are prioritised over others which can possibly lead to some misclassification. In the New Zealand statistics, Māoris are prioritised over Pacifics and Pacific people are prioritised over other ethnic groups. This means that if someone identifies as being both Chinese and Māori, for example, they would be classified as Māori in the statistics. Another limitation with prioritisation of ethnic groups is that it goes against the principle of self-identification (158). In a comparative study by the Ministry of Health in New Zealand, the prioritised ethnicity was compared with the total response ethnicity, and small differences were found (231). For the Asian ethnic groups, the only noticeable difference in standardized rate ratios for different health indicators was found for diabetes. The rate ratio for diabetes was lower for total response Asian versus the total New Zealand population, compared with the rate ratio of prioritised Asian versus prioritised European/other. For the other health indicators, the rate ratios were very similar (231).

Misclassification of endpoints

One of the limitations using registry data is that the data have been collected with another purpose than research, and that the researcher may lack information about content and quality of the variables (219). This means, among other things, that data could be affected by different coding practices between persons/institutions/time periods etc. However, any misclassification will often be non-differential since it will probably be the same for all subgroups and it will therefore most likely underestimate a true association or effect (219).

Both outcomes in paper 1, AMI and stroke, were identified through patient administrative systems in Norwegian hospitals and The Cause of Death Registry. We are not aware of any Norwegian

validation study to have validated the AMI diagnosis in patient administrative systems, but studies from other countries such as Denmark (232, 233) and the Netherlands (234) suggest that the positive predictive value is around 90% when AMI is coded as the main diagnosis and somewhat lower when AMI is coded as the secondary diagnosis. The definition of the AMI diagnosis was changed in Norwegian hospitals during 1999-2000 to include the use of troponin (235, 236). Compared with older diagnostic criteria, it has been shown that this change in diagnostic criteria increased the number of diagnosed AMI cases (237). It is possible that the change in AMI-definition during our study period could potentially bias the ethnic comparisons if some of the ethnic groups were particularly well represented in the Norwegian population after this period, while others were better represented before. However, as we adjusted for calendar year in the Poisson regression, we consider it as unlikely that this has had any considerable impact on our estimates.

Stroke discharge diagnoses in Norwegian hospital data have been validated for the Innherred region in Nord-Trøndelag county, in the central of Norway (238). The study compared data from hospital discharges using a population-based stroke registry as the "gold-standard". The study concluded that the use of hospital discharge data would overestimate stroke, unless restricting to acute stroke diagnoses which improved the positive predictive value from 49% to 68% (238). A more recent study, also carried out in the Central Norway region, used data from the Norwegian Stroke Registry to compare stroke admissions from the Norwegian Patient Registry (NPR) (239). The information from NPR, a national administrative health registry, is comparable to the hospital information from the CVDNOR project used in the present study. The study found that both the Norwegian Stroke Registry and the NPR were adequately complete and correct to be used as valuable sources in epidemiological studies. The NPR was more complete and less correct than the Stroke Registry when both main and secondary diagnoses of stroke were included with a positive predictive value of approximately 80%. If only including main stroke diagnoses, the registrations in NPR were more correct, but less complete with a positive predictive value well above 90% (239). Another recent validation study on intracranial haemorrhage supported that the coding of strokes from NPR is of good quality with positive predictive values > 90% (240). Both these recent validation studies found that the most common cause of incorrect diagnosis of acute stroke was previous stroke that should have been coded as rehabilitation or sequela after stroke (239, 240). This corresponds with what we observed in our data (paper 1) as we found more registered recurrent stroke events than recurrent AMI events, and several of the recurrent stroke events (especially for higher event numbers) had rehabilitation as main diagnosis and stroke as secondary diagnosis. We therefore suspected that some of these recurrent stroke events could be false positives representing previous strokes. Because we included more than one event per person, we decided to set a maximum limit of three

AMI and three stroke events per person to reduce the possibility of counting events more than once. A 28-day rule from the CVDNOR-project implied that hospitalisations or deaths within ≤28 days after a previous hospitalisation were considered as part of the previous event (214). This applied to both AMI and stroke. We also noticed that there were quite a few stroke deaths occurring between 29-60 days after a previous stroke hospitalisation. It is possible that those stroke deaths did not represent new events, but should have been coded as complications after a stroke. However, this type of stroke deaths (occurring 29-60 days after a previous stroke) only constituted <1% of the stroke events in our study population. We also did sensitivity analyses where we only included one event per person, and the results of these analyses were similar to the original analyses regarding the ethnic comparisons. We therefore consider it as unlikely that this could have had any considerable effect on the ethnic differences in stroke in paper 1.

In paper 2, we used a composite CVD endpoint mostly due to power considerations since there were few endpoints among the South Asians in the Norwegian cohort, especially for stroke. However, we also did some of the analyses for CHD specifically, which are included in the additional online supplementary file of the paper, table A9. Endpoints had already been defined in the dataset and the CVD outcome in the PREDICT data was different from the CVD outcome in the Norwegian data. We therefore combined available sub-endpoints from CONOR into a new CVD event that was more similar to the New Zealand CVD event, although some differences remained (which are provided in the paper). As our intention was to compare within the cohort and not across, we considered a small discrepancy in CVD endpoints between the two cohorts as acceptable. As already discussed, different CVD outcomes can be misclassified due to unreliable ICD-coding. Some of the included diagnoses in the composite CVD event, such as angina, heart failure (234) and peripheral arterial disease (241) have been found to be less reliable compared with acute and less diffuse diagnoses such as AMI (232-234) in studies from the Netherlands and Denmark.

In paper 3, we used the same composite endpoint as in paper 2. As the PREDICT total cardiovascular disease outcome was based on an ischemic cardiovascular disease outcome definition from the Framingham Study (242), this was the proper endpoint for our aim of validating a Framingham risk score. However, the possibilities of misclassified CVD events as discussed above for the New Zealand part of paper 2, also apply to this paper.

As mentioned, the prospective design in papers 2 and 3 reduces the possibility of differential misclassification of the exposure variables since the assessment of exposure was gathered at the beginning of the studies.

However, a phenomenon called "the regression dilution bias" implies that the application of initial measurements of risk factors in prospective cohort studies may lead to an underestimation of the strength of the real association between the average/usual levels of the risk factors and the outcome (243). This can be due to different factors such as measurement error or short-term biological variations (243). In addition, lifestyle changes or medical treatment may also lead to changes in risk factors. These factors can also have caused weaker associations between the major risk factors and the CVD outcome (244).

However, in paper 2 and paper 3 the BP measurements may, in particular, be prone to some information bias as BP measurements easily vary and can be affected by a range of factors in the environment of which the measurements are taken. Factors that can affect the BP measurements include (among others) the behaviour and posture of the individual/patient, the person who is taking the measurement as well as the device (245). This is also discussed in paper 2. For the Norwegian data in paper 2, the blood pressure measurements were taken according to a standard protocol which reduces the possibility of differential information bias. In the New Zealand data this was not the case, but a mean of the two last recordings done by the primary care practitioner was used for the systolic blood pressure variable to reduce the chance of information bias. Other risk factor variables (for example whether the patient had known hypertension or a high BMI without the appropriate cuff size) could potentially have affected the reliability of the blood pressure measurements (246).

Confounding

A confounder is a variable that has an effect on (or is associated with – but not affected by) both the exposure (or mediator) and the outcome (218). Paper 1 was descriptive in its intent and paper 3 had mainly a predictive purpose, the causal structures were therefore mostly relevant for paper 2.

We cannot rule out the possibility of unmeasured confounding for the prospective relationships between the conventional risk factors and CVD in paper 2 (Table 2) where possible confounders could be lifestyle-related factors such as diet or physical activity. We were not able to completely adjust for lifestyle, but we consider the adjustment for all the risk factors SBP, TC/HDL ratio,

smoking and diabetes (results not shown) to also involve a partial adjustment for lifestyle. The results of these full-adjusted models were similar to the results of the age-adjusted models.

Mediation

For our main analyses in paper 2 (Table 3), ethnicity was the exposure variable and it is not very likely that an extraneous factor can have affected the ethnicity of the study subjects. Thus, for these analyses, mediation was more relevant than confounding. The four major cardiovascular risk factors were considered mediators in the ethnicity (exposure) – CVD (outcome) relationship in paper 2 (Table 3). Also, for each of the ethnicity (exposure) - risk factor (mediator) relationships, factors such as diet or physical activity are considered additional mediators (see figure 9 below). We did not have information about lifestyle, but by adjusting for all the four risk factors in the full-adjusted model (last row in Table 3, paper 2), we consider to also have adjusted for some of the mediating effect of lifestyle. Any direct effect of lifestyle that does not go through the conventional risk factors (for example the effect of exercise on coagulation factors (247)) was, however, not adjusted for.
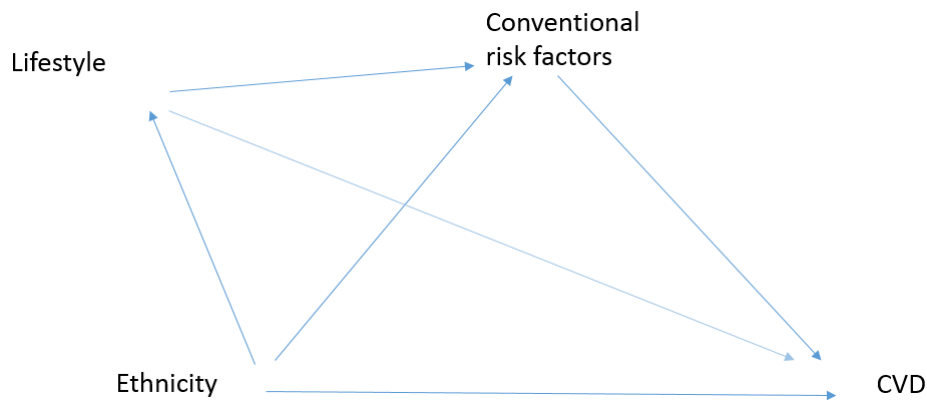
Figure 9. A simplified causal diagram for paper 2

Statistical power/precision

Some immigrant groups in paper 1 were small. We therefore presented the main results for regions instead of countries of birth. The Central Asia group in paper 1 had comparable risk of AMI as South Asians in both men and women, and we also found increased risk of stroke in women from Central Asia. However, the risk estimates were only based on eight AMI events and eight stroke events in Central Asian women and 34 AMI events in men from Central Asia with wide confidence intervals.

Thus, due to the lack of precision we chose not to highlight this increased risk among immigrants from Central Asia. Also in papers 2 and paper 3, the South Asian groups were small which resulted in imprecise estimates with wide confidence intervals. In paper 2, the lack of precision may have masked any potential interactions between the risk factors and ethnicity.

External validity/generalizability

Generalizations should be made with caution. However, given our considerations above, we consider the results from paper 1 to be generalizable to the young adult Norwegian population for the years covered by the study period, 1994-2009. The results may not be generalizable to future generations of immigrants or to later periods as the arrival of new immigrants or migrants leaving the country will change the composition of the groups that were included in this study. Even if the composition of the groups remained the same, the comparisons between ethnic groups can still change with time since the risk of CVD in a population might change, and also since years lived in a country may alter the risk of disease among immigrants. The increased risk of CVD (especially AMI) in South Asians, however, was evident and consistent in all three papers. The *sizes* of the relative risk estimates may not be generalizable to other settings, but otherwise, it seems reasonable to assume that the results of an increased risk in South Asians in Norway and New Zealand may also apply to South Asians in other settings. However, this does not necessarily apply equally to all South Asian subgroups.

For paper 2, we studied South Asians and Europeans who participated in three population-based health surveys in Norway. The groups were relatively small, but it is reassuring that the results were similar in the New Zealand data as in the Norwegian data. Results based on New Zealand data in paper 2 and 3 can be generalized to Indians and Europeans living in New Zealand who are eligible for cardiovascular risk assessments according to the New Zealand guidelines. As for paper 1, the results from paper 2 and 3 may not be generalizable for future generations of the ethnic groups that we studied.

5.2 General discussion of the results

In this section, I will discuss how the results compare with other studies in the existing literature of the relevant fields.

5.2.1 Ethnic variation in risk of AMI and stroke

In the nationwide prospective cohort study in paper 1, we found large variations in risk of both AMI and stroke between ethnic groups in Norway. South Asians had the highest risk of AMI and constituted the only ethnic group to have an increased risk of stroke in both men and women compared to ethnic Norwegians. Our finding of an increased risk of AMI and stroke in South Asians in Norway was in line with the knowledge about risk factor levels in immigrants from South Asia based on Norwegian health studies (161-164) and also in line with the knowledge from other countries about an excess risk of CVD (particularly CHD) in this ethnic group (18, 173, 179, 186-188, 248). The risk of stroke in South Asian migrants has been less studied, but a high risk of stroke among South Asians compared with Europeans has been documented in studies from the UK (18, 248) and in New Zealand (173). Furthermore, the increased risk in South Asians was reconfirmed in paper 2 in both Norwegian and New Zealand data, and also in the updated New Zealand cohort in paper 3 where we found that Indians and Europeans had similar observed 5-year event rates of CVD despite Europeans being 6-8 years older than the Indians. The finding of an increased risk of AMI in immigrant men and women from Former Yugoslavia and a high risk of stroke in immigrant men from Former Yugoslavia was consistent with a previous study where we found that Former Yugoslavian immigrants in Norway had the highest Framingham predicted risk scores among the eleven ethnic groups included in the study (162). International studies show conflicting results when it comes to the risk of CVD in immigrants from Former Yugoslavia compared with other ethnic groups. A registry-based study from Denmark found no differences in CVD between immigrants from Former Yugoslavia and persons born in Denmark (188). Similarly in Sweden, a case-control study covering the years 1977-1996 did not find any differences in risk of MI between immigrants from Former Yugoslavia and native Swedes (187). Another Swedish (registry-based) study, however, found an increased risk of first MI in men from Former Yugoslavia, women from Serbia and men and women from Bosnia compared with Swedish-born (249). In Austria, an increased risk of MI was found among young immigrants from Former Yugoslavia compared with native Austrians (250). An increased risk of stroke was also found among immigrants from Former Yugoslavia in Malmö, Sweden (251). The same study found an increased risk of stroke in immigrant women from China/Vietnam, which corresponds with our findings of increased risk of stroke in women from

44

Southeast Asia (which includes Vietnam). Some of the variation in rates of AMI and stroke between the immigrant groups found in paper 1 also seems to mirror the disease patterns in the countries of origin for the different immigrant groups, at least to some degree. For example, the GBD study report about a stroke-dominant CVD mortality pattern in countries from Southeast Asia, East Asia and Sub-Saharan Africa (100) which corresponds with our findings of a lower risk of AMI in immigrants from East Asia, Southeast Asia and Sub-Saharan Africa compared with Norwegian-born, while a lower risk of stroke was not observed. In fact, we found a higher risk of stroke in South East Asian women and Sub-Saharan men. The lower risk of AMI in the East Asia group also corresponds with a lower risk of CHD in immigrants from China that has been consistently documented in studies from different countries, such as Singapore (252), the UK (186), Canada (253) and the Netherlands (254). The lower risk of AMI and stroke among immigrants from Western Europe, Eastern Europe and North America is in line with the "healthy immigrant effect". To a large extent, immigrants from these countries came to Norway for work or education purposes (255), and the lower mortality that has been observed among immigrants compared with the Norwegian host population was most evident among those who had immigrated due to work/ education purposes (136).

5.2.2 Cardiovascular risk factors in South Asians (paper 2)

Our finding of similar and positive relationships between the major risk factors (SBP, TC/HDL ratio, smoking and diabetes) and subsequent CVD in South Asians and Europeans is in line with the two prospective studies that were available at the start of the present study (12, 13). It also corresponds with the large multinational case-control studies INTERHEART (14) and INTERSTROKE (15).Two other studies from the UK emerged during our work with the present study, and found consistent results of similar relationships between behavioural risk factors (19) and diabetes (20) with the risk of subsequent CVD. Another study, reported that diabetes was more predictive of stroke in South Asians than in Europeans (18), while a fourth study, also from the UK, found that BP was stronger associated with stroke risk in South Asian men than in European men (21). In the latter study, South Asian men had higher BP levels than European men, which conflicts with our findings of lower BP levels in South Asians in both Norway and New Zealand (21). The study also found that the combination of high BP and glycaemia seemed more detrimental in South Asians than in Europeans (21). Poorer cerebral autoregulation in South Asians than in Europeans due to more hyperglycaemia could be one of the underlying mechanisms for their excess risk of stroke (256). We did not study stroke specifically in paper 2, and can therefore not rule out the possibility that different relationships between some of the major risk factors and subsequent stroke exist between South

Asians and Europeans in New Zealand or Norway. However, the role of hyperglycaemia for the susceptibility of stroke in South Asians concur with a five to almost eight times higher (Norwegian cohort) and around three times higher (New Zealand cohort) prevalence of diabetes in South Asians versus Europeans in this study. It also corresponds with our main results where diabetes was one of two risk factors that were able to explain some of the excess risk of CVD in South Asians compared with Europeans. The reduction in the increased risk of CVD in South Asians versus Europeans after full adjustment ranged from 7-38% (based on the PERM calculation described in section 3.5). However, the highest PERM was achieved in the model where we only adjusted for diabetes and TC/ HDL ratio, where PERM ranged from 35-66% indicating that a significant share of the excess risk of CVD is mediated through diabetes and a poor lipid profile. However, although the lipid profile did explain some of the excess risk of CVD in South Asians in the Norwegian cohort, this was not the case in the New Zealand cohort - which should have been better pointed out in the paper. Adding TC/HDL ratio to the Cox regression model did not change the HRs for the excess risk of CVD for South Asians versus Europeans in the New Zealand cohort, which was also true for the model where CHD was the endpoint (Table A9 in the supplementary file in paper 2). This could be related to use of lipid lowering treatment, but adjusting for baseline medication did not change the full-adjusted HRs (Table A4 in the supplementary material in paper 2). Thus, diabetes (not lipids) seemed to explain some of the increased risk of CVD among South Asians in the New Zealand cohort. The finding of diabetes' important role for the excess risk of CVD in South Asians is in line with international studies highlighting the importance of diabetes when it comes to the risk of CVD in South Asians (18, 189, 256). A recent optimistic review article suggests that there have been improvements in treatment and management of diabetes in South Asians, which has now led to an attenuation in the increased CVD mortality risk in South Asians versus Europeans (257).

After we adjusted for the major risk factors (SBP, TC/HDL ratio, smoking and diabetes), South Asians still had an increased risk of CVD compared with Europeans in both the New Zealand and Norwegian cohorts. This concurs with findings from the UK (12, 18) where conventional (and some novel) risk factors did not seem to account for the excess risk of CVD in South Asians. However, as South Asians generally develop diabetes in younger age than Europeans (189), it is possible that we were unable to capture the full effect of diabetes since we lacked information about disease duration. For risk factors that fluctuate (TC/HDL ratio and SBP), the regression dilution effect (243, 244) could also contribute to explain some of the remaining excess risk in the full-adjusted model. Furthermore, we did not have information about physical activity, which another study found could explain around 40% of the excess CHD mortality among Pakistanis/Bangladeshis (combined in one group) and Indians when it was included as a covariate in a Cox model (13). Dietary habits may also

be an important explaining factor/mediator that we did not adjust for (206, 258).

5.2.3 Predicted Framingham risk in South Asians and the role of BMI and deprivation (paper 3)

In paper 3, we found that a Framingham risk score (242), published in 1991 and based on risk factors collected more than four decades ago, predicted the 5-year risk of CVD moderately close in Indian men in New Zealand, and overestimated risk in Indian women and in European men and women. The lack of studies reporting discrimination and calibration measures for the performance of existing cardiovascular risk scores among South Asians makes it difficult to compare results across the available studies. However, one study emerged during our work with this project which validated the same Framingham risk score as applied here, although for the prediction of 10-year risk instead of 5- year risk (84). This study was performed in the UK and found that Framingham underestimated the risk in South Asian women while it predicted risk more closely in South Asian men when a factor of 1.4 had been added to their predicted risk. AUCs were 0.73 [95% CI 0.69 to 0.77] in South Asian men and 0.77 [95% CI 0.69 to 0.86] in South Asian women, which is similar to the AUCs of 0.76 that we found in South Asian men and women and the CIs were overlapping. Thus, the discrimination measures were not very different from our results, but the calibration showed an underestimation of risk in South Asians (also in men had the factor of 1.4 not been added) instead of an overestimation of risk as was found among Indian women in our study. For Europeans, the Framingham 10-year risk score predicted reasonably well in both men and women (84). However, the results of this UK study is not directly comparable to the present study as we, as mentioned, validated risk prediction models with different time perspectives. We also found that social deprivation and BMI could potentially improve risk prediction. The UK study that evaluated Framingham, also evaluated QRISK2 (259) which includes a deprivation index (the Townsend score) corresponding to the New Zealand deprivation index and BMI (continuous) as predictors. QRISK2 underestimated risk in South Asian men and women, while it predicted risk more closely in European men and women (84). Thus, the study did not find that QRISK2 predicted risk more accurately than Framingham, as one would expect based on QRISK2's inclusion of BMI and deprivation, and since Framingham's validity in ethnically and socioeconomically diverse populations has been questioned (260-262).

Our finding of an overestimation of risk in European men and women as well as in Indian women could be related to medical treatment initiated after baseline measurements. We performed sensitivity analyses to test this where we reset the risk factor values for those who were dispensed antihypertensive and/or lipid lowering medication during follow-up according to treatment goals.

These sensitivity analyses resulted in small changes in calibration (Figure 7 in 4.1.4). Moreover, in a recent study, our New Zealand collaborators presented estimations of how much the observed risk could have changed due to any initiation of preventive medication during follow-up (226). Their calculations took into account the person-time that participants were on/off preventive treatment (lipid lowering, blood pressure lowering or antithrombotic) during follow-up, and they arrived at an estimate of 5% (in any decile) when optimistically assuming that a single additional medication would reduce risk by 25%. A change in risk of 5% is not very much, and not enough to explain the overestimated risk found in the present study. Thus, it is not likely that medical treatment during follow-up explains the overestimation of risk found in paper 3, although medical treatment is one of the contributing factors behind the low risk in the contemporary New Zealand population. Our findings demonstrate that improved methods for risk assessment in Europeans and Indians in New Zealand are warranted. Indeed, a new risk prediction score for the general New Zealand population was recently derived (and published) based on the same PREDICT data that we used in paper 3 (226). This new risk score includes the New Zealand deprivation index and ethnicity as predictors, but not BMI.

6.0 Conclusions and future studies

We studied the risk of CVD among immigrants in the Norwegian total population over a 16-year period. Immigrants were heterogeneous in terms of cardiovascular risk, and South Asians had a particularly high burden of AMI and stroke compared with ethnic Norwegians and other immigrant groups. Former Yugoslavians, immigrants from Central Asia and men from the Middle East also had a higher risk of CVD, which merits further attention. Men from Sub-Saharan Africa and women from Southeast Asia also had increased risk of stroke. The lowest risk of AMI was found in immigrants from East Asia.

We found that SBP, TC/HDL ratio, smoking and diabetes are important cardiovascular risk factors for both South Asians and Europeans. This was an expected, yet important finding due to the lack of prospective studies focusing on the relationship between conventional risk factors and later CVD in South Asian populations. Furthermore, the high risk of CVD in South Asians are in part a result of the increased diabetes prevalence in this ethnic group and poor lipid profile (the latter is at least relevant for the Norwegian setting). Primary prevention should therefore specifically aim to improve the prevention and management of diabetes and dyslipidaemia among South Asians.

The Framingham risk score overestimated risk in South Asian women and in European men and women, which demonstrates a need for improved methods for risk assessment in the New Zealand

context. The study also showed that BMI and deprivation are potentially useful predictors in addition to the Framingham predictors. A new risk model which includes ethnicity and the New Zealand deprivation index as predictors was recently made available for the New Zealand population (226). This new risk prediction model is likely to perform better than Framingham in both Indians and Europeans, but should be externally validated in Indians in the future given the high risk of CVD in this ethnic group.

Future research

The immigrant population is in constant change, which makes it necessary to regularly repeat descriptive studies, such as the one presented in paper 1. Norway has experienced a considerable change in its composition of immigrants after paper 1 was published, partly as a consequence of the war in Syria with Syrian refugees seeking asylum in Norway, and labour immigrants from Eastern European countries returning to their home countries (263). Updated information about risk factors among the immigrant population in Norway is needed as the available data, used in this thesis, were gathered for almost 20 years ago.

Whether the immigrant population has experienced the same decline in the incidence of AMI as the majority population, is unknown. Trends in CVD among the immigrant population should therefore be studied. Descendants of immigrants (Norwegian-born to immigrant parents) have so far been too young to study regarding CVD. Thus, an interesting and important research focus would be to examine the burden of disease in this population to see whether it resembles the burden of CVD in their parents' generation.

A new risk prediction model called NORRISK2 (264) has been developed for the prediction of the 10-year risk of incident acute myocardial infarction or cerebral stroke in the Norwegian population. This model replaced an older version which predicted the risk of CVD mortality. Neither diabetes nor ethnicity is included as predictors in NORRISK2, and the risk score has therefore been expected to underestimate the risk of AMI/stroke in South Asians. Adding a factor of 1.5 to the risk score for South Asians was recommended in the national Norwegian guidelines to compensate for this (265). We have now started to look at the data and, as expected, we find that NORRISK2 underestimate the 13-year risk of CVD (AMI or stroke) in South Asians. We plan to validate the NORRISK 2 among South Asians in Norway and to derive a new cardiovascular risk prediction model for this ethnic group.

References

1.	Bhopal RS. Ethnicity, race, and health in multicultural societies: foundations for better epidemiology, public health, and health care: Oxford University Press; 2007.
2.	World Health Organization. Cardiovascular diseases (CVDs). Fact Sheet: World Health Organization. [Updated May 2017, Retrieved March 2018]. Available from: www.who.int/mediacentre/factsheets/fs317/en/
3.	Meade TW. Cardiovascular disease—linking pathology and epidemiology. Int J Epidemiol. 2001;30(5):1179-83.
4.	Rasche H. Haemostasis and thrombosis: an overview. Eur Heart J Suppl. 2001;3(suppl_Q):Q3- Q7.
5.	Kumar V, Abbas AK, Aster JC. Blood vessels. In: Robbins Basic Pathology E-Book 10th edition: Elsevier Health Sciences; 2017.
6.	Lusis AJ. Atherosclerosis. Nature. 2000;407(6801):233-41.
7.	Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med. 1999;340(2):115-26.
8.	Hansson GK, Libby P. The immune response in atherosclerosis: a double-edged sword. Nat Rev Immunol. 2006;6(7):508-19.
9.	Kannel WB. Overview of hemostatic factors involved in atherosclerotic cardiovascular disease. Lipids. 2005;40(12):1215-20.
10.	Bhatnagar A. Environmental Determinants of Cardiovascular Disease. Circ Res. 2017;121(2):162-80.
11.	D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study. Circulation. 2008;117(6):743-53.
12.	Forouhi N, Sattar N, Tillin T, McKeigue P, Chaturvedi N. Do known risk factors explain the higher coronary heart disease mortality in South Asian compared with European men? Prospective follow-up of the Southall and Brent studies, UK. Diabetologia. 2006;49(11):2580- 8.
13.	Williams ED, Stamatakis E, Chandola T, Hamer M. Physical activity behaviour and coronary heart disease mortality among South Asian people in the UK: an observational longitudinal study. Heart. 2011;97(8):655-9.
14.	Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937-52.
15.	O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet. 2010;376(9735):112-23.
16.	Pais P, Pogue J, Gerstein H, Zachariah E, Savitha D, Jayprakash S, et al. Risk factors for acute myocardial infarction in Indians: a case-control study. Lancet. 1996;348(9024):358-63.
17.	Gerstein HC, Pais P, Pogue J, Yusuf S. Relationship of glucose and insulin levels to the risk of myocardial infarction: a case-control study. J Am Coll Cardiol. 1999;33(3):612-9.
18.	Tillin T, Hughes AD, Mayet J, Whincup P, Sattar N, Forouhi NG, et al. The Relationship Between Metabolic Risk Factors and Incident Cardiovascular Disease in Europeans, South Asians, and African Caribbeans: SABRE (Southall and Brent Revisited)—A Prospective Population-Based Study. J Am Coll Cardiol. 2013;61(17):1777-86.
19.	Eriksen A, Tillin T, O'Connor L, Brage S, Hughes A, Mayet J, et al. The Impact of Health Behaviours on Incident Cardiovascular Disease in Europeans and South Asians–A Prospective Analysis in the UK SABRE Study. PLoS One. 2015;10(3):1-15.
20.	Eastwood SV, Tillin T, Sattar N, Forouhi NG, Hughes AD, Chaturvedi N. Associations Between Prediabetes, by Three Different Diagnostic Criteria, and Incident CVD Differ in South Asians and Europeans. Diabetes Care. 2015;38(12):2325-32.
21.	Eastwood SV, Tillin T, Chaturvedi N, Hughes AD. Ethnic Differences in Associations Between

Blood Pressure and Stroke in South Asian and European Men. Hypertension. 2015;66(3):481- 8.

22. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. Nature. 2006;444(7121):875-80.

23. Iliodromiti S, Celis-Morales CA, Lyall DM, Anderson J, Gray SR, Mackay DF, et al. The impact of confounding on the associations of different adiposity measures with the incidence of cardiovascular disease: a cohort study of 296 535 adults of white European descent. Eur Heart J. 2018;39(17):1514–20.

24. Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009;373(9669):1083-96.

25. Dudina A, Cooney MT, Bacquer DD, Backer GD, Ducimetiere P, Jousilahti P, et al. Relationships between body mass index, cardiovascular mortality, and risk factors: a report from the SCORE investigators. Eur J Cardiovasc Prev Rehabil. 2011;18(5):731-42.

26. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. Geneva: World Health Organization; 2000. WHO technical report series; 894.

27. WHO expert consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363(9403):157-63.

28. Misra A. Ethnic-specific criteria for classification of body mass index: a perspective for Asian Indians and American Diabetes Association Position Statement. Diabetes Technol Therap. 2015;17(9):667-71.

29. Yajnik CS, Yudkin JS. The Y-Y paradox. Lancet. 2004;363(9403):163.

30. Misra A, Chowbey P, Makkar BM, Vikram NK, Wasir JS, Chadha D, et al. Consensus Statement for Diagnosis of Obesity, Abdominal Obesity and the Metabolic Syndrome for Asian Indians and Recommendations for Physical Activity, Medical and Surgical Management. J Assoc Physicians India. 2009;57:163-70.

31. Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G, et al., for the Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects). Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. Lancet. 2014;383(9921):970-83.

32. Lu Y, Hajifathalian K, Rimm EB, Ezzati M, Danaei G. Mediators of the effect of body mass index on coronary heart disease: decomposing direct and indirect effects. Epidemiology. 2015;26(2):153-62.

33. Blüher M. Are there still healthy obese patients? Curr Opin Endocrinol Diabetes Obes. 2012;19(5):341-6.

34. Alpert JS. "So, Doctor, What's So Bad About Being Fat?" Combating the Obesity Epidemic in the United States. Am J Med. 2010;123(1):1-2.

35. Lassale C, Tzoulaki I, Moons KGM, Sweeting M, Boer J, Johnson L, et al. Separate and combined associations of obesity and metabolic health with coronary heart disease: a pan-European case-cohort analysis. Eur Heart J. 2018;39(5):397-406.

36. Fan J, Song Y, Chen Y, Hui R, Zhang W. Combined effect of obesity and cardio-metabolic abnormality on the risk of cardiovascular disease: a meta-analysis of prospective cohort studies. Int J Cardiol. 2013;168(5):4761-8.

37. Bell JA, Hamer M, Sabia S, Singh-Manoux A, Batty GD, Kivimaki M. The Natural Course of Healthy Obesity Over 20 Years. J Am Coll Cardiol. 2015;65(1):101-2.

38. Norwegian Institute of Public Health. Overweight and obesity in Norway. In: Public Health Report (Online publications). Published 10 March 2011. [Updated 03 November 2017, Retrieved August 2018]. Available from: https://www.fhi.no/en/op/hin/risk--protective-factors/overweight-and-obesity-in-norway---/

39. Meyer HE, Tverdal A. Development of body weight in the Norwegian population. Prostaglandins Leukot Essent Fatty Acids. 2005;73(1):3-7.

40.   Jenum AK, Graff-Iversen S, Selmer R, Søgaard A-J. Risikofaktorer for hjerte-og karsykdom og diabetes gjennom 30 år. Tidsskr Nor Legeforen. 2007(127):2532–6.
41.   Norwegian Institute of Public Health. Cardiovascular disease in Norway. In: Public Health Report (Online publications). Published 06 April 2009. [Updated 18 April 2016, Retrieved May 2018]. Available from: https://www.fhi.no/en/op/hin/health--disease/cardiovascular-disease-in-norway---/
42.   McKeigue P, Shah B, Marmot M. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. Lancet. 1991;337(8738):382-6.
43.   Hughes K, Aw TC, Kuperan P, Choo M. Central obesity, insulin resistance, syndrome X, lipoprotein(a), and cardiovascular risk in Indians, Malays, and Chinese in Singapore. J Epidemiol Community Health. 1997;51(4):394-9.
44.   Raza Q, Snijder MB, Seidell JC, Peters RJ, Nicolaou M. Comparison of cardiovascular risk factors and dietary intakes among Javanese Surinamese and South-Asian Surinamese in the Netherlands. The HELIUS study. BMC Res Notes. 2017;10(1):23.
45.   Kumar B, Meyer H, Wandel M, Dalen I, Holmboe-Ottesen G. Ethnic differences in obesity among immigrants from developing countries, in Oslo, Norway. Int J Obes (Lond). 2006;30(4):684-90.
46.   Rush EC, Freitas I, Plank LD. Body size, body composition and fat distribution: comparative analysis of European, Maori, Pacific Island and Asian Indian adults. Br J Nutr. 2009;102(4):632-41.
47.   Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med. 2006;23(5):469-80.
48.   Yusuf S, Hawken S, Ôunpuu S, Bautista L, Franzosi MG, Commerford P, et al. Obesity and the risk of myocardial infarction in 27 000 participants from 52 countries: a case-control study. Lancet. 2005;366(9497):1640-9.
49.   Antonovsky A. Social class, life expectancy and overall mortality. Milbank Mem Fund Q. 1967;45(2):31-73.
50.   Marmot MG. Status syndrome: a challenge to medicine. JAMA. 2006;295(11):1304-7.
51.   Antonovsky A. Social class and the major cardiovascular diseases. J Chronic Dis. 1968;21(2):65-106.
52.   Kaplan GA, Keil JE. Socioeconomic factors and cardiovascular disease: a review of the literature. Circulation. 1993;88(4 Pt 1):1973-98.
53.   Marmot MG, Rose G, Shipley M, Hamilton PJ. Employment grade and coronary heart disease in British civil servants. J Epidemiol Community Health. 1978;32(4):244-9.
54.   Rose G, Marmot MG. Social class and coronary heart disease. Br Heart J. 1981;45(1):13-9.
55.   Morgenstern H. The changing association between social status and coronary heart disease in a rural population. Social Sci Med Med Psychol Med Sociol. 1980;14A(3):191-201.
56.   Avendano M, Kunst AE, Huisman M, Lenthe FV, Bopp M, Regidor E, et al. Socioeconomic status and ischaemic heart disease mortality in 10 western European populations during the 1990s. Heart. 2006;92(4):461-7.
57.   Avendano M, Kunst AE, Huisman M, van Lenthe F, Bopp M, Borrell C, et al. Educational level and stroke mortality: a comparison of 10 European populations during the 1990s. Stroke. 2004;35(2):432-7.
58.   Strand BH, Grøholt E-K, Steingrímsdóttir ÓA, Blakely T, Graff-Iversen S, Næss Ø. Educational inequalities in mortality over four decades in Norway: prospective study of middle aged men and women followed for cause specific mortality, 1960-2000. BMJ. 2010;340:c654.
59.   Ariansen I, Graff-Iversen S, Stigum H, Strand BH, Wills AK, Næss Ø. Do repeated risk factor measurements influence the impact of education on cardiovascular mortality? Heart. 2015;101(23):1889-94.
60.   Fawcett J, Blakely T, Kunst A. Are mortality differences and trends by education any better or worse in New Zealand? A comparison study with Norway, Denmark and Finland, 1980-

1990s. Eur J Epidemiol. 2005;20(8):683-91.

61.   Uphoff EP, Pickett KE, Wright J. Social gradients in health for Pakistani and White British women and infants in two UK birth cohorts. Ethn Health. 2016;21(5):452-67.

62.   Nazroo JY. South Asian people and heart disease: an assessment of the importance of socioeconomic position. Ethn Dis. 2001;11(3):401-11.

63.   Williams R, Wright W, Hunt K. Social class and health: the puzzling counter-example of British South Asians. Soc Sci Med. 1998;47(9):1277-88.

64.   Bos V, Kunst AE, Garssen J, Mackenbach JP. Socioeconomic inequalities in mortality within ethnic groups in the Netherlands, 1995–2000. J Epidemiol Community Health. 2005;59(4)329-35.

65.   Manrique-Garcia E, Sidorchuk A, Hallqvist J, Moradi T. Socioeconomic position and incidence of acute myocardial infarction: a meta-analysis. J Epidemiol Community Health. 2011;65(4):301-9.

66.   Ali MK, Bhaskarapillai B, Shivashankar R, Mohan D, Fatmi ZA, Pradeepa R, et al. Socioeconomic status and cardiovascular risk in urban South Asia: The CARRS Study. Eur J Prev Cardiol. 2016;23(4):408-19.

67.   Buttenheim A, Goldman N, Pebley AR, Wong R, Chung C. Do Mexican immigrants "import" social gradients in health to the US? Soc Sci Med. 2010;71(7):1268-76.

68.   Mackenbach JP, Cavelaars A, Kunst AE, Groenhof F. Socioeconomic inequalities in cardiovascular disease mortality; an international study. Eur Heart J. 2000;21(14):1141-51.

69.   Rogers EM. Diffusion of innovations. 4th ed. New York: The Free Press. A division of Simon and Schuster Inc; 2010.

70.   Agyemang C, van Oeffelen AA, Bots ML, Stronks K, Vaartjes I. Socioeconomic inequalities in acute myocardial infarction incidence in migrant groups: has the epidemic arrived? analysis of nation-wide data. Heart. 2014;100(3):239-46.

71.   Agyemang C, van Oeffelen AA, Norredam M, Kappelle LJ, Klijn CJ, Bots ML, et al. Socioeconomic inequalities in stroke incidence among migrant groups: analysis of nationwide data. Stroke. 2014;45(8):2397-403.

72.   Syed HR, Dalgard OS, Hussain A, Dalen I, Claussen B, Ahlberg NL. Inequalities in health: a comparative study between ethnic Norwegians and Pakistanis in Oslo, Norway. Int J Equity Health. 2006;5:7.

73.   Vedøy TF. The role of education for current, former and never-smoking among non-western immigrants in Norway. Does the pattern fit the model of the cigarette epidemic? Ethn Health. 2013;18(2):190-210.

74.   Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G. Indicators of socioeconomic position (part 2). J Epidemiol Community Health. 2006;60(2):95-101.

75.   Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G. Indicators of socioeconomic position (part 1). J Epidemiol Community Health. 2006;60(1):7-12.

76.   Townsend P. Deprivation. J Soc Policy. 1987;16(2):125-46.

77.   Salmond C, Crampton P. NZDep96 - What does it measure? Social Policy Journal of New Zealand. 2001;17:82-100.

78.   Bitton A, Gaziano TA. The Framingham Heart Study's Impact on Global Risk Assessment. Prog Cardiovasc Dis. 2010;53(1):68-78.

79.   Jackson R, Lawes CM, Bennett DA, Milne RJ, Rodgers A. Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk. Lancet. 2005;365(9457):434-41.

80.   Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016;37(29):2315-81.

81.   Ministry of Health. Cardiovascular Disease Risk Assessment and Management for Primary Care. Wellington, New Zealand: Ministry of Health; 2018. ISBN: 978-1-98-853933-1.

82.   World Health Organization. Prevention of Cardiovascular Disease. Pocket Guidelines for Assessment and Management of Cardiovascular Risk. (WHO/ISH Cardiovascular Risk Prediction Charts for WHO epidemiological sub-regions AFR D and AFR E) Geneva: World Health Organization; 2007. ISBN 978 92 4 154726 0.

83.   Altman DG, Vergouwe Y, Royston P, Moons KG. Prognosis and prognostic research: validating a prognostic model. BMJ. 2009;338:b605.

84.   Tillin T, Hughes AD, Whincup P, Mayet J, Sattar N, McKeigue PM, et al. Ethnicity and prediction of cardiovascular disease: performance of QRISK2 and Framingham scores in a U.K. tri-ethnic prospective cohort study (SABRE--Southall And Brent REvisited). Heart. 2014;100(1):60-7.

85.   Kandula NR, Kanaya AM, Liu K, Lee JY, Herrington D, Hulley SB, et al. Association of 10-year and lifetime predicted cardiovascular disease risk with subclinical atherosclerosis in South Asians: findings from the Mediators of Atherosclerosis in South Asians Living in America (MASALA) study. J Am Heart Assoc. 2014;3(5):e001117.

86.   Kanaya AM, Kandula N, Herrington D, Budoff MJ, Hulley S, Vittinghoff E, et al. Mediators of Atherosclerosis in South Asians Living in America (MASALA) study: objectives, methods, and cohort description. Clin Cardiol. 2013;36(12):713-20.

87.   Bhagat V, Baviskar S, Mudey AB, Goyal R. Prospective, longitudinal, cohort study for assessment of vascular ageing among adults of urban and rural area of Central India: research protocol. Int J Community Med Public Health. 2017;4(9):3273-8.

88.   Guha S, Basu AK, Pal SK, Chatterjee N, Guha S, Deb PK. Predictive efficacy of Framingham's risk score in Indian scenario--a retrospective case-control study. J Indian Med Assoc. 2004;102(10):568, 570, 584 passim.

89.   Bhopal R, Fischbacher C, Vartiainen E, Unwin N, White M, Alberti G. Predicted and observed cardiovascular disease in South Asians: application of FINRISK, Framingham and SCORE models to Newcastle Heart Project data. J Public Health (Oxf). 2005;27(1):93-100.

90.   Jaquet A, Deloumeaux J, Dumoulin M, Bangou J, Donnet JP, Foucan L. Metabolic syndrome and Framingham risk score for prediction of cardiovascular events in Caribbean Indian patients with blood glucose abnormalities. Diabetes Metab. 2008;34(2):177-81.

91.   Guha S, Pal SK, Chatterjee N, Guha S, Ghosh A, Deb PK. How predictive is the Framingham's risk prediction algorithm in Indian perspective? A retrospective case-control study from Kolkata. Indian Heart J. 2008;60(4):330-2.

92.   Bellary S, Paul O'Hare J, Raymond NT, Mughal S, Hanif WM, Jones A, et al. Premature cardiovascular events and mortality in south Asians with type 2 diabetes in the United Kingdom Asian Diabetes Study – effect of ethnicity on risk. Curr Med Res Opin. 2010;26(8):1873-9.

93.   GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1151-210.

94.   Global Health Estimates 2015: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2015. Geneva: World Health Organization; 2016.

95.   Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet. 2014;383(9913):245-54.

96.   Gaziano TA, Bitton A, Anand S, Abrahams-Gessel S, Murphy A. Growing epidemic of coronary heart disease in low-and middle-income countries. Curr Probl Cardiol. 2010;35(2):72-115.

97.   World Health Organization. Global status report on noncommunicable diseases 2010. World Health Organization; 2011. ISBN: 978 92 4 156422 9

98.   Kwan GF, Mayosi BM, Mocumbi AO, Miranda JJ, Ezzati M, Jain Y, et al. Endemic

Cardiovascular Diseases of the Poorest Billion. Circulation. 2016;133(24):2561-75.

99. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. J Am Coll Cardiol. 2017;70(1):1-25.

100. Roth GA, Huffman MD, Moran AE, Feigin V, Mensah GA, Naghavi M, et al. Global and regional patterns in cardiovascular mortality from 1990 to 2013. Circulation. 2015;132(17):1667-78.

101. Mathers CD, Salomon JA, Ezzati M, Begg S, Hoorn SV, Lopez AD. Sensitivity and Uncertainty Analyses for Burden of Disease and Risk Factor Estimates. In: Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL, editors. Global Burden of Disease and Risk Factors. Washington (DC): World Bank; 2006. Chapter 5.

102. India State-Level Disease Burden Initiative Collaborators. Nations within a nation: variations in epidemiological transition across the states of India, 1990–2016 in the Global Burden of Disease Study. Lancet. 2017;390(10111):2437-60.

103. Sulo G, Igland J, Nygård O, Vollset SE, Ebbing M, Tell GS. Favourable trends in incidence of AMI in Norway during 2001–2009 do not include younger adults: a CVDNOR project. Eur J Prev Cardiol. 2014;21(11):1358-64.

104. Sulo G, Igland J, Vollset SE, Ebbing M, Egeland GM, Ariansen I, et al. Trends in incident acute myocardial infarction in Norway: An updated analysis to 2014 using national data from the CVDNOR project. Eur J Prev Cardiol. 2018;25(10):1031-9.

105. Sulo E, Vollset SE, Nygård O, Sulo G, Igland J, Egeland GM, et al. Trends in 28-day and 1-year mortality rates in patients hospitalized for a first acute myocardial infarction in Norway during 2001-2009: a"Cardiovascular disease in Norway"(CVDNOR) project. J Intern Med. 2015;277(3):353-61.

106. Mannsverk J, Wilsgaard T, Mathiesen EB, Løchen M-L, Rasmussen K, Thelle DS, et al. Trends in Modifiable Risk Factors Are Associated With Declining Incidence of Hospitalized and Nonhospitalized Acute Coronary Heart Disease in a Population. Circulation. 2016;133(1):74-81.

107. Vangen-Lønne AM, Wilsgaard T, Johnsen SH, Carlsson M, Mathiesen EB. Time trends in incidence and case fatality of ischemic stroke: the tromsø study 1977-2010. Stroke. 2015;46(5):1173-9.

108. Carlsson M, Wilsgaard T, Johnsen SH, Vangen-Lønne AM, Løchen M-L, Njølstad I, et al. Temporal Trends in Incidence and Case Fatality of Intracerebral Hemorrhage: The Tromsø Study 1995-2012. Cerebrovasc Dis Extra. 2016;6(2):40-9.

109. Grey C, Jackson R, Wells S, Wu B, Poppe K, White H, et al. First and recurrent ischaemic heart disease events continue to decline in New Zealand, 2005–2015. Heart. 2018;104(1):51-7.

110. Chan WC, Wright C, Tobias M, Mann S, Jackson R. Explaining trends in coronary heart disease hospitalisations in New Zealand: trend for admissions and incidence can be in opposite directions. Heart. 2008;94(12):1589-93.

111. Feigin VL, Krishnamurthi RV, Barker-Collo S, McPherson KM, Barber PA, Parag V, et al. 30-Year Trends in Stroke Rates and Outcome in Auckland, New Zealand (1981-2012): A Multi-Ethnic Population-Based Series of Studies. PLoS One. 2015;10(8):e0134609.

112. Roth GA, Forouzanfar MH, Moran AE, Barber R, Nguyen G, Feigin VL, et al. Demographic and Epidemiologic Drivers of Global Cardiovascular Mortality. N Engl J Med. 2015;372(14):1333-41.

113. Ainsworth JD, Carruthers E, Couch P, Green N, O'Flaherty M, Sperrin M, et al. IMPACT: a generic tool for modelling and simulating public health policy. Methods Inf Med. 2011;50(5):454-63.

114. Capewell S, Beaglehole R, Seddon M, McMurray J. Explanation for the decline in coronary heart disease mortality rates in Auckland, New Zealand, between 1982 and 1993. Circulation. 2000;102(13):1511-6.

115. Capewell S, Morrison CE, McMurray JJ. Contribution of modern cardiovascular treatment

and risk factor changes to the decline in coronary heart disease mortality in Scotland between 1975 and 1994. Heart. 1999;81(4):380-6.

116. Critchley J, Liu J, Zhao D, Wei W, Capewell S. Explaining the increase in coronary heart disease mortality in Beijing between 1984 and 1999. Circulation. 2004;110(10):1236-44.

117. Kabir Z, Perry IJ, Critchley J, O'Flaherty M, Capewell S, Bennett K. Modelling Coronary Heart Disease Mortality declines in the Republic of Ireland, 1985-2006. Int J Cardiol. 2013;168(3):2462-7.

118. Pereira M, Azevedo A, Lunet N, Carreira H, O'Flaherty M, Capewell S, et al. Explaining the decline in coronary heart disease mortality in Portugal between 1995 and 2008. Circ Cardiovasc Qual Outcomes. 2013;6(6):634-42.

119. Unal B, Sözmen K, Arik H, Gerceklioglu G, Altun DU, Simsek H, et al. Explaining the decline in coronary heart disease mortality in Turkey between 1995 and 2008. BMC Public Health. 2013;13:1135.

120. Psota M, Bandosz P, Goncalvesova E, Avdicova M, Bucek Psenkova M, Studencan M, et al. Explaining the decline in coronary heart disease mortality rates in the Slovak Republic between 1993-2008. PLoS One. 2018;13(1):e0190090.

121. Tunstall-Pedoe H, Kuulasmaa K, Mähönen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. Lancet. 1999;353(9164):1547-57.

122. Hopstock LA, Bønaa KH, Eggen AE, Grimsgaard S, Jacobsen BK, Løchen ML, et al. Longitudinal and secular trends in total cholesterol levels and impact of lipid-lowering drug use among Norwegian women and men born in 1905-1977 in the population-based Tromsø Study 1979- 2016. BMJ open. 2017;7(8):e015001.

123. Hopstock LA, Bønaa KH, Eggen AE, Grimsgaard S, Jacobsen BK, Løchen ML, et al. Longitudinal and Secular Trends in Blood Pressure Among Women and Men in Birth Cohorts Born Between 1905 and 1977: The Tromsø Study 1979 to 2008. Hypertension. 2015;66(3):496- 501.

124. Krokstad S, Knudtsen MS. Public health development. The HUNT Study, Norway: HUNT 1 (1984-86) – HUNT 2 (1995-97) – HUNT 3 (2006-08). [Folkehelse i endring. Helseundersøkelsen Nord-Trøndelag HUNT 1 (1984-86) – HUNT 2 (1995-97) – HUNT 3 (2006- 08)]. Levanger: HUNT Research Centre; 2011.

125. Ruiz PLD, Stene LC, Bakken IJ, Håberg SE, Birkeland KI, Gulseth HL. Decreasing incidence of pharmacologically and non-pharmacologically treated type 2 diabetes in Norway: a nationwide study. Diabetologia. 2018. doi: 10.1007/s00125-018-4681-4. [Epub ahead of print]

126. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. Circulation. 2001;104(22):2746-53.

127. Omran AR. The epidemiologic transition. A theory of the epidemiology of population change. Milbank Mem Fund Q. 1971;49(4):509-38.

128. Gaziano T, Reddy KS, Paccaud F, Horton S, Chaturvedi V. Cardiovascular Disease. In: Jamison DT, Breman JG, Measham AR, Alleyne G, Claseson M, Evans DB, et al., editors. Disease Control Priorities in Developing countries. 2nd edition. Washintong (DC): World Bank. NewYork: Oxford University Press; 2006. Chapter 33.

129. Geldsetzer P, Manne-Goehler J, Theilmann M, Davies JI, Awasthi A, Vollmer S, et al. Diabetes and hypertension in India: a nationally representative study of 1.3 million adults. JAMA Intern Med. 2018;178(3):363-72.

130. Joshi SR. Type 2 diabetes in Asian Indians. Clin Lab Med. 2012;32(2):207-16.

131. The Oxford English Dictionary. Migration. Oxford University Press; 2018. Retrieved July 2018 from: http://www.oed.com/view/Entry/118324?redirectedFrom=migration#eid

132. Holmboe-Ottesen G, Wandel M. Changes in dietary habits after migration and

consequences for health: a focus on South Asians in Europe. Food Nutr Res. 2012;56. doi: 10.3402/fnr.v56i0.18891. Epub 2012 Nov 6.

133. Carballo M, Mboup M. International migration and health. A paper prepared for the Policy Analysis and Research Programme of the Global Commission on International Migration. 2005. Retrieved Aug 2018 from: https://www.iom.int/jahia/webdav/site/myjahiasite/shared/shared/mainsite/policy_and_res earch/gcim/tp/TP13.pdf

134. Castaneda H, Holmes SM, Madrigal DS, Young ME, Beyeler N, Quesada J. Immigration as a social determinant of health. Annu Rev Public Health. 2015;36:375-92.

135. Van Hear N, Bakewell O, Long K. Drivers of migration. Migrating out of Poverty RPC Working Paper 1. Migrating out of Poverty Consortium. Brighton, UK: University of Sussex; 2012. Available from: https://assets.publishing.service.gov.uk/media/57a08a7fed915d622c000787/WP1_Drivers_o f_Migration.pdf

136. Syse A, Dzamarija MT, Kumar BN, Diaz E. An observational study of immigrant mortality differences in Norway by reason for migration, length of stay and characteristics of sending countries. BMC Public Health. 2018;18(1):508.

137. Krieger N. Discrimination and Health Inequities. Int J Health Serv. 2014;44(4):643-710.

138. MIPEX. Migrant Integration Policy Index 2015. [Retrived April 2018] Available from: http://www.mipex.eu.

139. Villund O. Overqualification among immigrants in Norway 2007–2012. [Overkvalifisering blant innvandrere 2007-2012]. Oslo: Statistics Norway; 2014. Reports 2014/28. ISBN 978-82- 537-8984-2 (electronic).

140. Midtbøen AH, Rogstad JC. The extent and causes of discrimination. Ethnic minorities' access to employment in Norway (own translation). [Diskrimineringens omfang og årsaker. Etniske minoriteters tilgang til norsk arbeidsliv]. Report 1/12. Oslo: Institutt for samfunnsforskning; 2012. Available from: https://brage.bibsys.no/xmlui/bitstream/handle/11250/177445/R_2012_1_web.pdf?sequen ce=3&isAllowed=y

141. Wilson MG, Parker P. The gap between immigration and employment: A policy-capturing analysis of ethnicity-driven selection biases. New Zealand Journal of Employment Relations (Online). 2007;32(1):28.

142. Syse A, Strand BH, Naess O, Steingrímsdóttir ÓA, Kumar BN. Differences in all-cause mortality: A comparison between immigrants and the host population in Norway 1990-2012. Demogr Res. 2016;34(22):615-56.

143. Norredam M, Olsbjerg M, Petersen JH, Juel K, A. K. Inequalities in mortality among refugees and immigrants compared to native Danes - a historical prospective cohort study. BMC Public Health. 2012;12:757.

144. Hajat A, Blakely T, Dayal S, Jatrana S. Do New Zealand's immigrants have a mortality advantage? Evidence from the New Zealand Census-Mortality Study. Ethn Health. 2010;15(5):531-47.

145. Abraido-Lanza AF, Dohrenwend BP, Ng-Mak DS, Turner JB. The Latino mortality paradox: a test of the "salmon bias" and healthy migrant hypotheses. Am J Public Health. 1999;89(10):1543-8.

146. Sorlie PD, Backlund E, Johnson NJ, Rogot E. Mortality by Hispanic status in the United States. JAMA. 1993;270(20):2464-8.

147. Rosenwaike I. Mortality differentials among persons born in Cuba, Mexico, and Puerto Rico residing in the United States, 1979-81. Am J Public Health. 1987;77(5):603-6.

148. Domnich A, Panatto D, Gasparini R, Amicizia D. The "healthy immigrant" effect: does it exist in Europe today? Ital J Public Health. 2012;9(3).

149. Fuller-Thomson E, Brennenstuhl S, Cooper R, Kuh D. An investigation of the healthy migrant hypothesis: Pre-emigration characteristics of those in the British 1946 birth cohort study.

Can J Public Health. 2016;106(8):e502-e8.

150. Puschmann P, Robyn Donrovich R, Matthijs K. Salmon Bias or Red Herring? Comparing Adult Mortality Risks (ages 30-90) between Natives and Internal Migrants: Stayers, Returnees and Movers in Rotterdam, the Netherlands, 1850–1940. Hum Nat. 2017;28(4):481-99.

151. Norredam M, Hansen OH, Petersen JH, Kunst AE, Kristiansen M, Krasnik A. Remigration of migrants with severe disease: myth or reality? - a register-based cohort study. Eur J public health. 2015;25(1):84-9.

152. Wallace M, Kulu H. Can the salmon bias effect explain the migrant mortality advantage in England and Wales? Popul Space Place. 2018:e2146. doi:10.1002/psp.2146

153. Turra CM, Elo IT. The impact of salmon bias on the Hispanic mortality advantage: New evidence from social security data. Popul Res Policy Rev. 2008;27(5):515-30.

154. Moullan Y, Jusot F. Why is the 'healthy immigrant effect' different between European countries? Eur J Public Health. 2014;24 Suppl 1:80-6

155. Vang ZM, Sigouin J, Flenon A, Gagnon A. Are immigrants healthier than native-born Canadians? A systematic review of the healthy immigrant effect in Canada. Ethn Health. 2017;22(3):209-41.

156. Shor E, Roelfs D, Vang ZM. The "Hispanic mortality paradox" revisited: Meta-analysis and meta-regression of life-course differentials in Latin American and Caribbean immigrants' mortality. Soc Sci Med. 2017;186:20-33.

157. Statistics New Zealand. Statistical Standard for Ethnicity 2005. [Retrieved August 2018]. Available from:
http://archive.stats.govt.nz/browse_for_stats/population/census_counts/review-measurement-of-ethnicity.aspx.

158. Ministry of Health. Ethnicity Data Protocols for the Health and Disability Sector. Wellington: Ministry of Health; 2004.

159. Brochmann G, Kjeldstadli K. A history of immigration: the case of Norway 900-2000: Universitetsforlaget; 2008.

160. Statistics Norway. 14 per cent of population are immigrants. Published 5 March 2018. [Retrieved May 2018]. Available from: https://www.ssb.no/en/befolkning/artikler-og-publikasjoner/14-per-cent-of-population-are-immigrants

161. Kumar BN, Selmer R, Lindman A, Tverdal A, Falster K, Meyer H. Ethnic differences in SCORE cardiovascular risk in Oslo, Norway. Eur J Cardiovasc Prev Rehabil. 2009;16(2):229 - 34.

162. Rabanal KS, Lindman AS, Selmer RM, Aamodt G. Ethnic differences in risk factors and total risk of cardiovascular disease based on the Norwegian CONOR study. Eur J Prev Cardiol. 2013;20(6):1013-21.

163. Glenday K, Kumar BN, Tverdal A, Meyer HE. Cardiovascular disease risk factors among five major ethnic groups in Oslo, Norway: the Oslo Immigrant Health Study. Eur J Cardiovasc Prev Rehabil. 2006;13(3):348-55.

164. Jenum AK, Diep LM, Holmboe-Ottesen G, Holme IM, Kumar BN, Birkeland KI. Diabetes susceptibility in ethnic minority groups from Turkey, Vietnam, Sri Lanka and Pakistan compared with Norwegians - the association with adiposity is strongest for ethnic minority women. BMC Public Health. 2012;12:150.

165. Gholap N, Davies M, Patel K, Sattar N, Khunti K. Type 2 diabetes and cardiovascular disease in South Asians. Prim Care Diabetes. 2011;5(1):45-56.

166. Smith PM. A concise history of New Zealand: Cambridge University Press; 2012.

167. Singham M. Multiculturalism in New Zealand – the need for a new paradigm. Aotearoa Ethnic Network Journal. 2006;1(1).

168. OECD (2018), Foreign-born population (indicator). doi: 10.1787/5a368e1b-en [Retrieved 10 June 2018].

169. Statistics New Zealand. 2013 Census – Major ethnic groups in New Zealand. Published 28 January 2015. [Retrieved May 2018]. Available from:
http://archive.stats.govt.nz/Census/2013-census/profile-and-summary-reports/infographic-

culture-identity.aspx

170. Statistics New Zealand. 2013 Census QuickStats about culture and identity. Asian ethnic group. [Retrieved May 2018]. Available from: http://archive.stats.govt.nz/Census/2013-census/profile-and-summary-reports/quickstats-culture-identity/asian.aspx

171. Statistics New Zealand. 2013 Census. Ethnic group profile: Indian. [Retrieved May 2018]. Available from: http://www.stats.govt.nz/Census/2013-census/profile-and-summary-reports/ethnic-profiles.aspx?request_value=24743&parent_id=24726&tabname=#2013

172. Statistics New Zealand. Travel and Migration to and from India: 1990–2010. (International Travel and Migration Articles). Wellington: Statistics New Zealand; 2011. Available from: http://archive.stats.govt.nz/browse_for_stats/population/Migration/travel-migration-india-1990-2010.aspx

173. Ministry of Health. Asian Health Chart Book 2006. Wellington, New Zealand; 2006. Public Health Intelligence Monitoring Report No.4. ISBN 0-478-29962-1 (Internet).

174. Perumal L, Wells S, Ameratunga S, Pylypchuk RD, Elley CR, Riddell T, et al. Markedly different clustering of CVD risk factors in New Zealand Indian and European people but similar risk scores (PREDICT-14). Aust N Z J Public Health. 2012;36(2):141-4.

175. Worldometers. Southern Asia population. [Retrieved June 2018]. Worldometers info; 2018. Available from: http://www.worldometers.info/world-population/southern-asia-population/

176. Sattar N, Gill JM. Type 2 diabetes in migrant south Asians: mechanisms, mitigation, and management. Lancet Diabetes Endocrinol. 2015;3(12):1004-16.

177. McKeigue PM, Miller G, Marmot M. Coronary heart disease in south Asians overseas: a review. J Clin Epidemiol. 1989;42(7):597-609.

178. Zaman MJ, Bhopal RS. New answers to three questions on the epidemic of coronary mortality in south Asians: incidence or case fatality? Biology or environment? Will the next generation be affected? Heart. 2013;99(3):154-8.

179. Fedeli U, Cestari L, Ferroni E, Avossa F, Saugo M, Modesti PA. Ethnic inequalities in acute myocardial infarction hospitalization rates among young and middle-aged adults in Northern Italy: high risk for South Asians. Intern Emerg Med. 2018;13(2):177-82.

180. Das A, Ambale-Venkatesh B, Lima JA, Freedman JE, Spahillari A, Das R, et al. Cardiometabolic disease in South Asians: A global health concern in an expanding population. Nutr Metab Cardiovasc Dis. 2017;27(1):32-40.

181. Tu JV, Chu A, Rezai MR, Guo H, Maclagan LC, Austin PC, et al. Incidence of Major Cardiovascular Events in Immigrants to Ontario, Canada: The CANHEART Immigrant Study. Circulation. 2015;132(16):1549-59.

182. Danaraj TJ, Acker MS, Danaraj W, Wong HO, Tan BY. Ethnic group differences in coronary heart disease in Singapore: An analysis of necropsy records. Am HeartJ. 1959;58(4):516-26.

183. Balarajan R, Bulusu L, Adelstein A, Shukla V. Patterns of mortality among migrants to England and Wales from the Indian subcontinent. Br Med J (Clin Res Ed). 1984;289(6453):1185-7.

184. Balarajan R. Ethnic differences in mortality from ischaemic heart disease and cerebrovascular disease in England and Wales. BMJ. 1991;302(6776):560-4.

185. Fischbacher CM, Bhopal R, Povey C, Steiner M, Chalmers J, Mueller G, et al. Record linked retrospective cohort study of 4.6 million people exploring ethnic variations in disease: myocardial infarction in South Asians. BMC Public Health. 2007;7:142.

186. Bansal N, Fischbacher CM, Bhopal RS, Brown H, Steiner MF, Capewell S. Myocardial infarction incidence and survival by ethnic group: Scottish Health and Ethnicity Linkage retrospective cohort study. BMJ open. 2013;3(9):e003415.

187. Hedlund E, Lange A, Hammar N. Acute myocardial infarction incidence in immigrants to Sweden. Country of birth, time since immigration, and time trends over 20 years. Eur J Epidemiol. 2007;22(8):493-503.

188. Hempler NF, Larsen FB, Nielsen SS, Diderichsen F, Andreasen AH, Jorgensen T. A registry-

based follow-up study, comparing the incidence of cardiovascular disease in native Danes and immigrants born in Turkey, Pakistan and the former Yugoslavia: do social inequalities play a role? BMC Public Health. 2011;11:662.

189.	Tillin T, Chaturvedi N. Stemming the tide of type 2 diabetes and its consequences in south Asian individuals. Lancet Diabetes Endocrinol. 2014;2(3):186-8.

190.	Joshi P, Islam S, Pais P, Reddy S, Dorairaj P, Kazmi K, et al. Risk factors for early myocardial infarction in South Asians compared with individuals in other countries. JAMA. 2007;297(3):286-94.

191.	Goyal A, Yusuf S. The burden of cardiovascular disease in the Indian subcontinent. Indian J Med Res. 2006;124(3):235-44.

192.	Srinath Reddy K, Shah B, Varghese C, Ramadoss A. Responding to the threat of chronic diseases in India. Lancet. 2005;366(9498):1744-9.

193.	Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med. 2008;359(1):61-73.

194.	Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia. 1992;35(7):595-601.

195.	Barker DJ. Fetal origins of coronary heart disease. BMJ. 1995;311(6998):171-4.

196.	Lindsay RS, Bennett PH. Type 2 diabetes, the thrifty phenotype – an overview. Br Med Bull. 2001;60(1):21-32.

197.	Forsdahl A. Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? Br J Prev Soc Med. 1977;31(2):91-5.

198.	Yajnik C, Fall CH, Coyaji KJ, Hirve SS, Rao S, Barker DJ et al. Neonatal anthropometry: the thin- fat Indian baby. The pune maternal nutrition study. Int J Obes Relat Metab Disord. 2003;27(2):173 - 80.

199.	Sletner L, Nakstad B, Yajnik CS, Mørkrid K, Vangen S, Vårdal MH, et al. Ethnic differences in neonatal body composition in a multi-ethnic population and the impact of parental factors: a population-based cohort study. PloS One. 2013;8(8):e73058.

200.	Modi N, Thomas EL, Uthaya SN, Umranikar S, Bell JD, Yajnik C. Whole body magnetic resonance imaging of healthy newborn infants demonstrates increased central adiposity in Asian Indians. Pediatr Res. 2009;65(5):584-7.

201.	van Steijn L, Karamali NS, Kanhai HH, Ariens GA, Fall CH, Yajnik CS, et al. Neonatal anthropometry: thin-fat phenotype in fourth to fifth generation South Asian neonates in Surinam. Int J Obes (Lond). 2009;33(11):1326-9.

202.	Karamali NS, Ariens GA, Kanhai HH, de Groot CJ, Tamsma JT, Middelkoop BJ. Thin-fat insulin- resistant phenotype also present in South Asian neonates born in the Netherlands. J Dev Orig Health Dis. 2015;6(1):47-52.

203.	Yajnik CS, Lubree HG, Rege SS, Naik SS, Deshpande JA, Deshpande SS, et al. Adiposity and Hyperinsulinemia in Indians Are Present at Birth. J Clin Endocrinol Metab. 2002;87(12):5575- 80.

204.	Sniderman AD, Bhopal R, Prabhakaran D, Sarrafzadegan N, Tchernof A. Why might South Asians be so susceptible to central obesity and its atherogenic consequences? The adipose tissue overflow hypothesis. Int J Epidemiol. 2007;36(1):220-5.

205.	Wells JC. Commentary: Why are South Asians susceptible to central obesity? — the El Niño hypothesis. Int J Epidemiol. 2007;36(1):226-7.

206.	Kakde S, Bhopal RS, Bhardwaj S, Misra A. Urbanized South Asians' susceptibility to coronary heart disease: The high-heat food preparation hypothesis. Nutrition. 2017;33:216-24.

207.	Bhopal RS, Rafnsson SB. Could mitochondrial efficiency explain the susceptibility to adiposity, metabolic syndrome, diabetes and cardiovascular diseases in South Asian populations? Int J Epidemiol. 2009;38(4):1072-81.

208.	Watve MG, Yajnik CS. Evolutionary origins of insulin resistance: a behavioral switch hypothesis. BMC Evol Biol. 2007;7:61.

209.	Bakker LE, Boon MR, van der Linden RA, Arias-Bouda LP, van Klinken JB, Smit F, et al. Brown

adipose tissue volume in healthy lean south Asian adults compared with white Caucasians: a prospective, case-controlled observational study. Lancet Diabetes Endocrinol. 2014;2(3):210- 7.

210.   Boon MR, Bakker LE, van der Linden RA, van Ouwerkerk AF, de Goeje PL, Counotte J, et al. High prevalence of cardiovascular disease in South Asians: Central role for brown adipose tissue? Crit Rev Clin Lab Sci. 2015;52(3):150-7.

211.   Anand SS, Yusuf S, Vuksan V, Devanesen S, Teo KK, Montague PA, et al. Differences in risk factors, atherosclerosis, and cardiovascular disease between ethnic groups in Canada: the Study of Health Assessment and Risk in Ethnic groups (SHARE). Lancet. 2000;356(9226):279-84.

212.   Gupta S, Gudapati R, Gaurav K, Bhise M. Emerging risk factors for cardiovascular diseases: Indian context. Indian J Endocrinol Metab. 2013;17(5):806-14.

213.   Dodani S. Coronary Artery Diseases in South Asian Immigrants: An Update on High Density Lipoprotein Role in Disease Prevention. J Immigr Min Health. 2009;11(5):415-21.

214.   Igland J, Tell GS, Ebbing M, Nygård O, Vollset SE, Dimoski T. CVDNOR Data and Quality Report: The CVDNOR project: Cardiovascular Disease in Norway 1994 ‐ 2009. Description of data and data quality. 2013.

215.   Sulo G, Igland J, Vollset SE, Nygård O, Øyen N, Tell GS. Cardiovascular disease and diabetes mellitus in Norway during 1994-2009 CVDNOR - a nationwide research project. Norsk epidemiologi. 2013;23(1).

216.   Wells S, Riddell T, Kerr A, Pylypchuk R, Chelimo C, Marshall R, et al. Cohort Profile: The PREDICT Cardiovascular Disease Cohort in New Zealand Primary Care (PREDICT-CVD 19). Int J Epidemiol. 2017;46(1):22.

217.   Næss Ø, Søgaard AJ, Arnesen E, Beckstrøm AC, Bjertness E, Engeland A, et al. Cohort Profile: Cohort of Norway (CONOR). Int J Epidemiol. 2008;37(3):481-5.

218.   Rothman KJ, Greenland S, Lash TL. Validity in Epidemiologic studies. In: Rothman KJ, Greenland S, Lash TL, editors. Modern Epidemiology 3rd edition: Wolters Kluwer Health/Lippincott Williams and Wilkins; 2008. p. 128-47.

219.   Thygesen LC, Ersbøll AK. When the entire population is the sample: strengths and limitations in register-based epidemiology. Eur J Epidemiol. 2014;29(8):551-8.

220.   Boström G, Hallqvist J, Haglund BJ, Romelsjö A, Svanström L, Diderichsen F. Socioeconomic differences in smoking in an urban Swedish Population. The bias introduced by non-participation in a mailed questionnaire. Scand J Soc Med. 1993;21(2):77-82.

221.   Langhammer A, Krokstad S, Romundstad P, Heggland J, Holmen J. The HUNT study: participation is associated with survival and depends on socioeconomic status, diseases and symptoms. BMC Med Res Methodol. 2012;12:143.

222.   Nohr EA, Frydenberg M, Henriksen TB, Olsen J. Does low participation in cohort studies induce bias? Epidemiology. 2006;17(4):413-8.

223.   Søgaard A, Selmer R, Bjertness E, Thelle D. The Oslo Health Study: The impact of self-selection in a large population-based survey. Int J Equity Health. 2004;3(3).

224.   New Zealand Guideline Group. The assessment and Management of Cardiovascular Risk. Wellington, New Zealand 2003. Available from: https://www.health.govt.nz/system/files/documents/publications/cvd_risk_full.pdf

225.   Allen and Clarke. 2016. More Heart and Diabetes Checks Evaluation. Wellington: Ministry of Health. Available from: http://www.health.govt.nz/publication/more-heart-and-diabetes-checks-evaluation

226.   Pylypchuk R, Wells S, Kerr A, Poppe K, Riddell T, Harwood M, et al. Cardiovascular disease risk prediction equations in 400 000 primary care patients in New Zealand: a derivation and validation study. Lancet. 2018;391(10133):1897-907.

227.   Wells S, Poppe K, Selak V, Kerr A, Pylypchuk R, Wu B, et al. Is general practice identification of prior cardiovascular disease at the time of CVD risk assessment accurate and does it

matter? N Z Med J. 2018;131(1475):10-20.

228. Rothman KJ. Dealing with Biases. In: Rothman KJ. Epidemiology: An introduction 2nd edition: Oxford university press; 2012. p. 124-47.

229. Stronks K, Kulu-Glasgow I, Agyemang C. The utility of 'country of birth'for the classification of ethnic groups in health research: the Dutch experience. Ethn Health. 2009;14(3):255-69.

230. Senior PA, Bhopal R. Ethnicity as a variable in epidemiological research. BMJ. 1994;309(6950):327.

231. Ministry of Health. Presenting Ethnicity: Comparing prioritised and total response ethnicity in descriptive analyses of New Zealand Health Monitor surveys. Public Health Intelligence Occasional Bulletin No. 48. Wellington: Ministry of Health; 2008.

232. Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M. The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. J Clin Epidemiol. 2003;56(2):124-30.

233. Joensen AM, Jensen MK, Overvad K, Dethlefsen C, Schmidt E, Rasmussen L, et al. Predictive values of acute coronary syndrome discharge diagnoses differed in the Danish National Patient Registry. J Clin Epidemiol. 2009;62(2):188-94.

234. Merry AH, Boer JM, Schouten LJ, Feskens EJ, Verschuren WM, Gorgels AM, et al. Validity of coronary heart diseases and heart failure based on hospital discharge and mortality data in the Netherlands using the cardiovascular registry Maastricht cohort study. Eur J Epidemiol. 2009;24(5):237-47.

235. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. Eur Heart J. 2000;21(18):1502-13.

236. Hagen TP, Anthun KS, Reikvam A. Acute myocardial infarctions in Norway 1991-2001. [Hjerteinfarkt i Norge 1991 – 2007]. Tidsskrift Nor Laegeforening. 2010;130(8):820-4.

237. Langørgen J, Ebbing M, Igland J, Vollset SE, Nordrehaug JE, Tell GS, et al. Implications of changing definitions of myocardial infarction on number of events and all-cause mortality: the WHO 1979, ESC/ACC 2000, AHA 2003, and Universal 2007 definitions revisited. Eur J Prev Cardiol. 2014;21(11):1349-57.

238. Ellekjaer H, Holmen J, Krüger O, Terent A. Identification of incident stroke in Norway: hospital discharge data compared with a population-based stroke register. Stroke. 1999;30(1):56-60.

239. Varmdal T, Bakken IJ, Janszky I, Wethal T, Ellekjaer H, Rohweder G, et al. Comparison of the validity of stroke diagnoses in a medical quality register and an administrative health register. Scand J Public Health. 2016;44(2):143-9.

240. Øie LR, Madsbu MA, Giannadakis C, Vorhaug A, Jensberg H, Salvesen Ø, et al. Validation of intracranial hemorrhage in the Norwegian Patient Registry. Brain Beh. 2018;8(2):e00900.

241. Lasota AN, Overvad K, Eriksen HH, Tjønneland A, Schmidt EB, Grønholdt MM. Validity of Peripheral Arterial Disease Diagnoses in the Danish National Patient Registry. Eur J Vasc Endovasc Surg. 2017;53(5):679-85.

242. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. Am Heart J. 1991;121 (1 Pt 2):293-8.

243. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903-13.

244. Lewington S, Thomsen T, Davidsen M, Sherliker P, Clarke R. Regression dilution bias in blood total and high-density lipoprotein cholesterol and blood pressure in the Glostrup and Framingham prospective studies. J Cardiovasc Risk. 2003;10(2):143-8.

245. Tolonen H, Koponen P, Naska A, Männistö S, Broda G, Palosaari T, et al. Challenges in standardization of blood pressure measurement at the population level. BMC Med Res Methodol. 2015;15:33.

246. Ogedegbe G, Pickering T. Principles and techniques of blood pressure measurement Cardiol Clin. 2010;28(4):571-86.

247. Buttar HS, Li T, Ravi N. Prevention of cardiovascular diseases: Role of exercise, dietary interventions, obesity and smoking cessation. Exp Clin Cardiol. 2005;10(4):229-249.

248. Wild SH, Fischbacher C, Brock A, Griffiths C, Bhopal R. Mortality from all causes and circulatory disease by country of birth in England and Wales 2001-2003. J Public Health (Oxf). 2007;29(2):191-8.

249. Yang D, Dzayee DA, Beiki O, de Faire U, Alfredsson L, Moradi T. Incidence and case fatality after day 28 of first time myocardial infarction in Sweden 1987-2008. (Supplementary material). Eur J Prev Cardiol. 2012;19(6):1304-15.

250. Wiesbauer F, Blessberger H, Goliasch G, Holy EW, Pfaffenberger S, Tentzeris I, et al. Elevated risk of myocardial infarction in very young immigrants from former Yugoslavia. Eur J Epidemiol. 2009;24(11):691-6.

251. Khan FA, Zia E, Janzon L, Engstrom G. Incidence of stroke and stroke subtypes in Malmö, Sweden, 1990-2000: marked differences between groups defined by birth country. Stroke. 2004;35(9):2054-8.

252. Lee J, Heng D, Chia KS, Chew SK, Tan BY, Hughes K. Risk factors and incident coronary heart disease in Chinese, Malay and Asian Indian males: the Singapore Cardiovascular Cohort Study. Int J Epidemiol. 2001;30(5):983-8.

253. Nijjar AP, Wang H, Quan H, Khan NA. Ethnic and sex differences in the incidence of hospitalized acute myocardial infarction: British Columbia, Canada 1995-2002. BMC Cardiovasc Disord. 2010;10:38.

254. van Oeffelen AA, Vaartjes I, Stronks K, Bots ML, Agyemang C. Sex disparities in acute myocardial infarction incidence: Do ethnic minority groups differ from the majority population? Eur J Prev Cardiol. 2015; 22(2):180-8.

255. Østby L. The population with an immigrant background in 13 municipalities in Norway. Oslo: Statistics Norway; 2015. Reports 2015/04. ISBN 978-82-537-9067-1 (electronic).

256. Bathula R, Hughes AD, Panerai RB, Potter JF, Mc GTSA, Tillin T, et al. South Asians have adverse cerebrovascular haemodynamics, despite equivalent blood pressure, compared with Europeans. This is due to their greater hyperglycaemia. Int J Epidemiol. 2011;40(6):1490-8.

257. Johns E, Sattar N. Cardiovascular and Mortality Risks in Migrant South Asians with Type 2 Diabetes: Are We Winning the Battle? Curr Diab Rep. 2017;17(10):100.

258. Misra A, Khurana L, Isharwal S, Bhardwaj S. South Asian diets and insulin resistance. Br J Nutr. 2009;101(4):465-73.

259. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, May M, Brindle P. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. BMJ. 2007;335(7611):136.

260. Fiscella K, Tancredi D, Franks P. Adding socioeconomic status to Framingham scoring to reduce disparities in coronary risk assessment. Am Heart J. 2009;157(6):988-94.

261. Brindle PM, McConnachie A, Upton MN, Hart CL, Davey Smith G, Watt GC. The accuracy of the Framingham risk-score in different socioeconomic groups: a prospective study. Br J Gen Pract. 2005;55(520):838-45.

262. Brindle P, May M, Gill P, Cappuccio F, D'Agostino R Sr, Fischbacher C, et al. Primary prevention of cardiovascular disease: a web-based risk score for seven British black and minority ethnic groups. Heart. 2006;92(11):1595-602.

263. Statistics Norway. 05476: Migrations. Immigration, emigration and net migration, by citizenship 2003–2017. Statistics Norway; 2018. [Retrieved June 2018]. Available from: https://www.ssb.no/en/statbank/table/05476/tableViewLayout1/?rxid=3382138f- ab31-4136-950e-c4125b455a95

264. Selmer R, Igland J, Ariansen I, Tverdal A, Njølstad I, Furu K, et al. NORRISK 2: A Norwegian risk model for acute cerebral stroke and myocardial infarction. Eur J Prev Cardiol.

2017;24(7):773-82

265.   Norwegian Directorate of Health. National guidelines for prevention of cardiovascular disease. [Nasjonal faglig retningslinje for forebygging av hjerte- og karsykdom]. Oslo: Norwegian Directorate of H65ealth; 2017

Errata

P.5, line 20: "…patients, however, does not…" was changed to "…patients, however, do not…"

P.11, line 19: "…GBD estimates is.." was changed to "…GBD estimates are…"

P.12, line 10: "…no change were found…" was changed to "…no change was found…"

P.32, Figure 7: The y-axis values had been displaced during conversion to pdf-format before submission. The figure was corrected before printing.

P. 33, line 26: "Paper 3 share the strength…" was changed to "Paper 3 shares the strength…"

P.34, line 6: "Also, sine Norway is…" was changed to "Also, since Norway is…"

P.36, line 22: "…have experience…" was changed to "…have experienced…"

P.39, line 12: "…diagnoses…has been validated…" was changed to "…diagnoses…have been validated…"

P.47, line 20: "perspecitves" was changed to "perspectives"

I

BMC
Public Health

RESEARCH ARTICLE

Open Access

CrossMark

Ethnic inequalities in acute myocardial infarction and stroke rates in Norway 1994–2009: a nationwide cohort study (CVDNOR)

Kjersti S. Rabanal[1*], Randi M. Selmer[1], Jannicke Igland[2], Grethe S. Tell[2,3] and Haakon E. Meyer[1,4]

Abstract

Background: Immigrants to Norway from South Asia and Former Yugoslavia have high levels of cardiovascular disease (CVD) risk factors. Yet, the incidence of CVD among immigrants in Norway has never been studied. Our aim was to study the burden of acute myocardial infarction (AMI) and stroke among ethnic groups in Norway.

Methods: We studied the whole Norwegian population (*n* = 2 637 057) aged 35–64 years during 1994–2009. The Cardiovascular Disease in Norway (CVDNOR) project provided information about all AMI and stroke hospital stays for this period, as well as deaths outside hospital through linkage to the Cause of Death Registry. The direct standardization method was used to estimate age standardized AMI and stroke event rates for immigrants and ethnic Norwegians. Rate ratios (RR) with ethnic Norwegians as reference were calculated using Poisson regression.

Results: The highest risk of AMI was seen in South Asians (men RR = 2.27; 95 % CI 2.08–2.49; women RR = 2.10; 95 % CI 1.76–2.51) while the lowest was seen in East Asians (RR = 0.38 in both men (95 % CI 0.25–0.58) and women (95 % CI 0.18–0.79)). Immigrants from Former Yugoslavia and Central Asia also had increased risk of AMI compared to ethnic Norwegians. South Asians had increased risk of stroke (men RR = 1.26; 95 % CI 1.10–1.44; women RR = 1.58; 95 % CI 1.32–1.90), as did men from Former Yugoslavia, Sub-Saharan Africa and women from Southeast Asia.

Conclusions: Preventive measures should be aimed at reducing the excess numbers of CVD among immigrants from South Asia and Former Yugoslavia.

Keywords: Acute myocardial infarction, Cardiovascular disease, CVDNOR, Immigrants, Ethnicity, Stroke

Background

Europe has become a multi-ethnic continent with increasing migration across borders. Ethnic minority and migrant populations consequently make up substantial proportions of European populations [1]. The immigrants in Europe are heterogeneous in relation to age, sex, country of birth, socioeconomic status, type of migration, and they also vary in risk of cardiovascular diseases (CVD) [2]. In Norway overall, approximately 13 % of the population are immigrants compared to 32 % in the capital Oslo [3]. A large proportion of these immigrants comes from developing countries where the rates of CVD are rapidly increasing [3, 4]. Immigrants from South Asia (countries

such as Pakistan, Sri Lanka, India and Bangladesh) have a higher risk of coronary heart disease (CHD) as compared to local populations and other immigrant groups in the United Kingdom (UK), Denmark and Sweden [5–8]. Increased risk of CHD in South Asians in other parts of the world has also been reported [9, 10], suggesting a possible underlying susceptibility for CHD in this group. South Asian immigrants are prone to diabetes and metabolic disturbances such as abdominal adiposity, dyslipidaemia and hyperglycaemia [11], this has also been documented among South Asians in Norway [12, 13]. Still, the burden of CVD among this immigrant group is currently unknown.

Few studies have assessed the risk of CVD among immigrants from Former Yugoslavia (including countries such as Croatia, Slovenia, Bosnia-Hercegovina, Macedonia, Serbia, Montenegro and Kosovo) settled

* Correspondence: kjersti.stormark.rabanal@fhi.no
[1]Division of Epidemiology, Norwegian Institute of Public Health, P.O. Box 4404, Nydalen 0403 Oslo, Norway
Full list of author information is available at the end of the article

Rabanal *et al. BMC Public Health* (2015) 15:1073

Page 2 of 10

in Western European countries. Previous studies from Denmark and Sweden report no marked differences in incidence of CVD between Former Yugoslavian immigrants and the native populations [6, 8]. A more recent Swedish study, however, found higher incidence of first time acute myocardial infarction (AMI) in male immigrants from Former Yugoslavia compared to native Swedes [14]. A recent Danish study also found higher risk of CHD among immigrants from Former Yugoslavia compared to native Danes [15]. According to a Framingham risk calculator, immigrants from Former Yugoslavia in Norway have been found to have increased predicted 10-year risk of CVD compared to other ethnic groups [16]. Whether the predicted risk reflects actual risk of disease in this immigrant group is currently unknown.

The incidence of CVD among immigrants in Norway has never been reported. This nationwide study aimed to describe the burden of acute myocardial infarction and stroke among immigrants in Norway, compared to ethnic Norwegians.

Methods

Cardiovascular disease in Norway: the CVDNOR project

The CVDNOR project contains CVD hospitalization data for the whole Norwegian population for the period 1994–2009. Hospital stays with ICD9 codes 390–459 or ICD10 codes I00-I99 were extracted from the Patient Administrative Systems in all Norwegian somatic hospitals from 1994 to 2009 (www.cvdnor.no). The database includes information on age, sex, dates of hospitalization and discharge, main and secondary diagnoses, procedures, departments, wards, time of transfers between departments/wards and type of hospitalization. It has been linked to The Cause of Death Registry, and The Population Registry containing demographic and socioeconomic data for all subjects. Further details on this database are given elsewhere [17, 18].

Due to the young age distribution among immigrants in Norway, we included individuals aged 35–64 years (N = 2 652 123) at risk of having an AMI or stroke during 1994–2009. Country of birth was used to identify immigrants (born abroad with at least one parent born abroad). We therefore excluded persons with missing information on country of birth (n = 1 310), and individuals with a foreign country of birth whose parents were both born in Norway (n = 13 746). Some small countries were also excluded (St. Helena (n = 5), the British Indian Ocean Territory (n = 1), the Maldives (n = 2) and the Falkland Islands (n = 2)), leaving a total sample of 2 637 057 individuals for analyses. The population at risk was updated January 1st each year during 1994–2009. We grouped the immigrants into 14 larger regions (see Additional file 1: Table A1). Countries of birth with sufficient numbers were also analyzed individually in addition to the regions.

We identified hospitalizations with AMI (ICD9: 410; ICD10: I21, I22) or stroke (ICD9: 430, 431, 434, 436; ICD10: I60, I61, I63, I64) as main or secondary diagnosis and deaths outside hospital with AMI or stroke as underlying cause of death. For each individual, we included up to 3 events. However, a few individuals contributed with more than 3 events (maximum 6 events) if they had at least 7 event-free years between their third and fourth event. Most of the individuals experienced only one event (88 % of the individuals with AMI and 80 % of the individuals with stroke) during the study period, and 99.9 % experienced ≤ 3 events (both endpoints separately). Additional events were excluded to reduce the possibility of counting events more than once. For the same reason, we only included events with stroke as secondary diagnosis when the main diagnosis was other than rehabilitation. Hospitalizations or deaths occurring ≤ 28 days after a previous hospitalization were considered part of the previous event.

Statistical analyses

AMI and stroke event rates were calculated using the number of events (numerator) divided by the number of person-years from the population at risk during 1994–2009 (denominator). Persons aged 35–64 contributed with one person-year to the denominator every year they were registered (on January the 1st) as Norwegian residents. Age-standardized AMI and stroke event rates with 95 % confidence intervals (CIs) were computed using the direct standardization method, [19] stratified by ethnic group and expressed per 100 000 person-years. The Norwegian population of year 2001 was used as standard population and 5-year age strata were used for the standardization.

Poisson or negative binomial regression analyses (when goodness of fit test for the Poisson model was significant) were used to compute rate ratios (RRs) enabling us to control for calendar year to account for time trends in AMI and stroke. Ethnic Norwegians was the reference group and we adjusted for age in 5-year age groups and for calendar year as indicator variable. All analyses were performed in Stata 13.

Sensitivity analyses

We repeated the Poisson regression analyses including only 1 event during the whole period to see whether it influenced the estimates.

In addition to the main analyses, we have also calculated AMI and stroke event rates for a wider age group; 35–89 (see Additional file 1: Tables A2 and A3).

Attributable fractions

We calculated the attributable fractions (AF) for groups with increased risk of AMI and stroke (immigrants from South Asia and Former Yugoslavia) using the following

Rabanal *et al. BMC Public Health* (2015) 15:1073

Page 3 of 10

formula: AF = (RR-1)/RR [20]. The AFs indicate how much the event rates would have been reduced if the immigrant group had the same risk as ethnic Norwegians. RRs from the Poisson regression model were used in the calculation.

Ethical considerations

The project was approved by the Regional Committee for Medical Research Ethics, Health Region West.

Results

During 1994–2009, 1 348 744 women and 1 288 313 men aged 35–64 resided in Norway. Immigrants from 14 different regions totalled 282 485 subjects (45 % women), which constituted approximately 11 % of the study sample.

During the study period, we observed 67 683 AMI events in 59 314 individuals (20 % women) of whom 3 726 were immigrants. Correspondingly for stroke, we observed 43 252 events in 34 392 individuals (37 % women) whereof 2 078 were immigrants.

Acute myocardial infarction

In Table 1, we show age-standardized AMI event rates for regions and countries of birth. The overall crude AMI rates were 389 per 100 000 person-years in men and 101 per 100 000 person-years in women. Men from all regions had higher standardized rates than their female counterparts, and for most regions this gender difference was 3-fold. For most of the ethnic groups this gender difference was statistically significant (the CIs did not overlap), whereas for three small groups (China, Central America and Oceania/Pacific) the confidence intervals were wide and overlapping.

RRs for AMI, adjusted for age and calendar year, are shown in Fig. 1. Compared to ethnic Norwegians, immigrants from South Asia had the highest risk of AMI which was more than 2-fold in both men and women.

Immigrants from Central Asia had comparable AMI risk as the South Asians, but the CIs for the estimates were wide demonstrating uncertainty.

Immigrant men from Former Yugoslavia and the Middle East had around 50 % increased risk compared to Norwegian men, and immigrant women from Former Yugoslavia had a 75 % increased risk compared to ethnic Norwegian women.

Among countries of birth within South Asia (Sri Lanka, India and Pakistan), immigrants from Pakistan had the highest event rates of AMI. Men from Sri Lanka and India also had high rates compared to ethnic Norwegians (Table 1).

East Asian immigrants had the lowest risk of AMI with a RR of 0.38 for both men and women (Fig. 1). Immigrants from North America, Western Europe, and Southeast Asia, and immigrant women from Eastern Europe also had

lower risk of AMI compared to the local population in Norway. Immigrants from North Africa and Sub-Saharan Africa had reduced risk of AMI, although not statistically significant in women.

Stroke

In Table 2, we show age-standardized rates of stroke for regions and countries of birth. The overall crude stroke rates were 193 per 100 000 person-years in men and 116 per 100 000 person-years in women.

As for AMI, men had generally higher rates of stroke compared to women, although this was not true for immigrants from Southeast Asia, Central Asia and Central America, where women had similar rates as their male counterparts.

RRs for stroke, adjusted for age and calendar year, are shown in Fig. 2. In general, the ethnic differences in stroke risk were less consistent across genders compared to the differences in risk of AMI. For example, men from Former Yugoslavia and men from Sub-Saharan Africa had significantly higher risk of stroke compared to ethnic Norwegians (RRs of 1.28; 95 % CI 1.09–1.49 and 1.44; 95 % CI 1.20–1.74 respectively) but women from these regions did not have higher risk.

Immigrants from South Asia formed the only group with increased risk of stroke in both genders.

Reduced risk of stroke was seen in immigrant men from North Africa and North America. Slightly reduced risk was also observed in Eastern European men and Western European women.

Attributable fractions

If South Asians had the same risk as ethnic Norwegians, their risk would have been 52.4 % and 55.9 % lower than their observed risk, corresponding to a reduction of 63 out of 121 and 431 out of 771 cases of AMI (in women and men respectively) during the 16-year study period. In immigrants from Former Yugoslavia, the corresponding fractions were 42.9 % (representing 40 out of 94 AMI cases) in women and 33.3 % (representing 125 out of 374 AMI cases) in men. The AFs for stroke were 36.7 % in South Asian women and 20.6 % in South Asian men. For Former Yugoslavian men, the AF for stroke was 21.9 %. We did not calculate the AF for stroke in women from Former Yugoslavia since we did not find increased risk of stroke in this group.

Sensitivity analyses

The sensitivity analyses including only 1 AMI or stroke event per person had little influence on the estimates.

We found similar risk patterns for AMI in the wider age group, 35–89, as we did in our main analyses (see Additional file 1: Table A2). For stroke, the risk pattern was somewhat different when including the wider age

Rabanal *et al. BMC Public Health* (2015) 15:1073

Page 4 of 10

Table 1 Age standardized AMI event rates per 100 000 person-years, subjects aged 35–64 years, CVDNOR 1994–2009

Country or region of birth	Men, *n* = 1 288 313			Women, *n* = 1 348 744		
	N	AMIs	SER (95 % CI)	N	AMIs	SER (95 % CI)
Norway	1 194 414	50469	385 (382–388)	1 160 158	12891	98 (96–100)
Western Europe	56 603	1361	339 (321–357)	45 521	262	67 (59–75)
Denmark	10 581	314	352 (313–391)	9 474	54	56 (41–71)
Finland	3 248	99	434 (348–519)	3 889	20	63 (35–90)
Sweden	12 417	303	348 (308–387)	11 285	74	79 (61–97)
The Netherlands	2 938	46	259 (183–334)	2 221	9	55 (19–91)
Great Britain	9 955	226	300 (261–339)	5 511	49	93 (67–119)
Germany	8 339	178	357 (305–409)	6 552	29	53 (34–73)
Eastern Europe	23 031	220	376 (324–427)	14 550	42	67 (46–88)
Poland	15 698	105	357 (275–440)	5 599	21	67 (37–98)
Russia	1 429	13	349 (145–553)	4 188	3	29 (0–62)
Hungary	832	48	399 (276–521)	571	9	139 (46–231)
Former Yugoslavia	9 805	374	549 (491–606)	8 763	94	176 (140–213)
Bosnia-Hercegovina	4 437	196	537 (461–614)	4 470	57	176 (130–222)
Kosovo	2 790	82	869 (646–1092)	2 130	18	255 (112–398)
Middle East	15 710	402	513 (456–571)	9 445	48	123 (86–160)
Turkey	3 651	114	510 (409–610)	2377	22	166 (93–239)
Iraq	5 323	110	581 (454–709)	2759	9	94 (25–164)
Iran	4 882	127	438 (345–530)	3 245	11	80 (31–130)
North Africa	4 078	55	233 (167–299)	1 803	5	47 (0–95)
Morocco	2 260	32	210 (133–287)	1 198	3	50 (00–113)
Sub-Saharan Africa	10 497	126	259 (206–312)	7 052	17	98 (49–147)
Somalia	3 583	50	405 (265–545)	2 490	6	142 (28–255)
South Asia	13 063	771	812 (752–871)	10 238	121	216 (176–257)
Sri Lanka	3 623	120	707 (550–863)	2 834	6	46 (2–90)
India	2 447	99	514 (411–616)	1 911	17	163 (84–243)
Pakistan	6 115	538	978 (894–1061)	4 967	95	283 (224–342)
Southeast Asia	6 280	102	253 (202–305)	14 304	31	49 (30–69)
Philippines	1 227	30	344 (219–469)	4 642	10	53 (15–92)
Vietnam	4 303	62	223 (164–283)	4 161	8	32 (9–54)
East Asia	2 775	22	165 (94–235)	3 460	7	43 (11–75)
China	1 763	13	137 (62–213)	1 987	5	64 (8–120)
Central Asia	1 347	34	733 (461–1005)	1 195	8	218 (65–371)
North America	5 812	72	226 (173–279)	5 867	18	50 (27–73)
USA	5 025	64	228 (171–284)	5 012	10	31 (12–51)
Central America	710	11	267 (111–424)	1 032	6	140 (21–259)
South America	3 870	84	302 (233–371)	4 342	22	86 (48–125)
Chile	2 472	67	328 (242–413)	1 999	10	63 (22–103)
Oceania/Pacific	749	6	255 (49–462)	583	2	50 (0–120)

AMI acute myocardial infarction, *SER* standardized event rate; *CI* confidence interval

group. Among men, immigrants from Eastern Europe constituted the only group with significantly increased risk of stroke (according to the 95 % confidence intervals) compared to ethnic Norwegians (see Additional file 1: Table A3). Among women, immigrants from Former Yugoslavia had significantly increased risk of stroke

Rabanal *et al. BMC Public Health* (2015) 15:1073

Page 5 of 10

Region of birth	RR (95% CI)
Men	
Norway	1.00 (reference)
Western Europe	0.88 (0.81, 0.95)
Eastern Europe	0.98 (0.85, 1.14)
Former Yugoslavia	1.50 (1.33, 1.69)
Middle East	1.45 (1.29, 1.62)
North Africa	0.61 (0.46, 0.80)
Sub–Saharan Africa	0.80 (0.66, 0.96)
South Asia	2.27 (2.08, 2.49)
Southeast Asia	0.64 (0.52, 0.78)
East Asia	0.38 (0.25, 0.58)
Central Asia	1.95 (1.38, 2.74)
North America	0.58 (0.46, 0.74)
Central America	0.66 (0.36, 1.20)
South America	0.82 (0.66, 1.02)
Oceania/Pacific	0.49 (0.22, 1.10)
Women	
Norway	1.00 (reference)
Western Europe	0.68 (0.60, 0.77)
Eastern Europe	0.65 (0.48, 0.88)
Former Yugoslavia	1.75 (1.43, 2.15)
Middle East	1.20 (0.91, 1.60)
North Africa	0.63 (0.26, 1.52)
Sub–Saharan Africa	0.77 (0.48, 1.24)
South Asia	2.10 (1.76, 2.51)
Southeast Asia	0.47 (0.33, 0.67)
East Asia	0.38 (0.18, 0.79)
Central Asia	2.18 (1.09, 4.36)
North America	0.51 (0.32, 0.80)
Central America	1.30 (0.59, 2.90)
South Ameria	0.90 (0.60, 1.37)
Oceania/Pacific	0.55 (0.14, 2.22)

Fig. 1 Forest plot showing incidence rate ratios for AMI events in subjects aged 35–64 years. The rate ratios are adjusted for age and calendar year

compared to ethnic Norwegians, and immigrants from South Asia had an excess risk that was borderline significant according to the confidence intervals.

Discussion

This is the first study to describe the burden of CVD among immigrants in Norway. Our study showed that ethnic groups vary in risk of AMI and stroke, and identified differences in absolute and relative risk. Particularly immigrants from South Asia and Former Yugoslavia were found to have increased risk of AMI compared to other ethnic groups. Despite the relatively young population, we found high numbers of attributable cases in these two immigrant groups. The high numbers illustrate potential benefits from prevention in these high-risk groups. When compared to ethnic Norwegians, immigrants from Western Europe, North America, East Asia and Southeast Asia had reduced risk of AMI, both men and women. Only immigrants from South Asia had increased risk of stroke in both men and women.

Immigrants from South Asia had the highest risk of AMI, more than two-fold compared to ethnic Norwegians.

They also had increased risk of stroke. This corresponds well with previous Norwegian studies reporting high levels of cardiovascular risk factors among South Asian immigrants [13, 16, 21, 22]. It was also concordant with the UK literature reporting a particularly high risk of CHD and a higher risk of stroke in immigrants from South Asia compared to the general UK population [5, 7, 23]. While elevated risk of CHD in South Asian populations has been documented in several countries around the world [24], the risk of stroke in this immigrant group has received less focus, especially outside the UK. Within the UK, however, immigrants from South Asia have been found to have increased risk of stroke compared to the native European population in England and Wales, but not in Scotland [25, 26]. The latter possibly due to high stroke rates in the white Scottish comparison population. South Asians come from a region with a high prevalence of stroke, especially in the urban areas. It has been stated that South Asia probably contributes to more than 40 % of the worlds' stroke related deaths [27]. This fraction is, however, somewhat uncertain, since there is a general lack of population-based studies on the occurrence of stroke in

Rabanal *et al. BMC Public Health* (2015) 15:1073
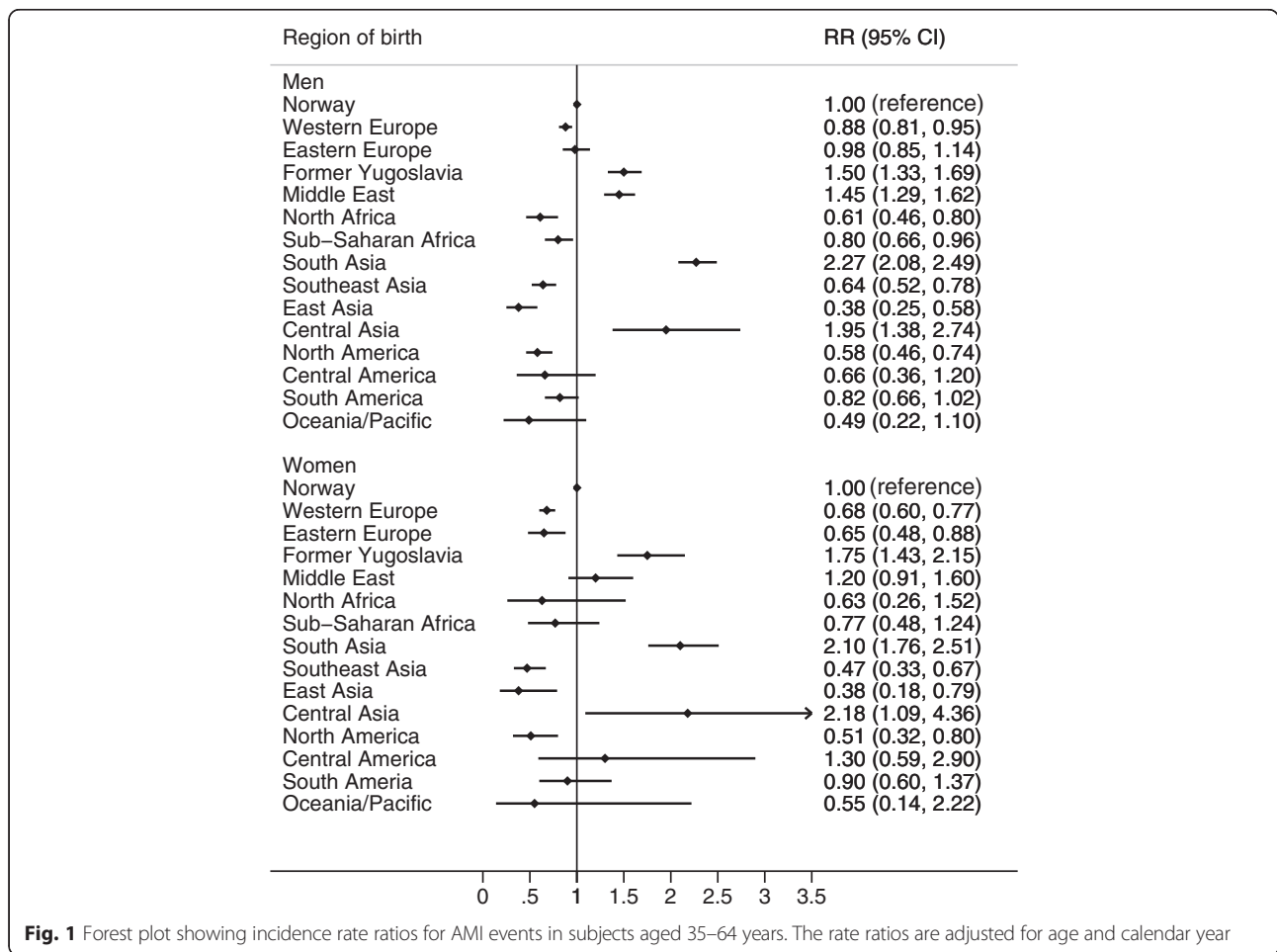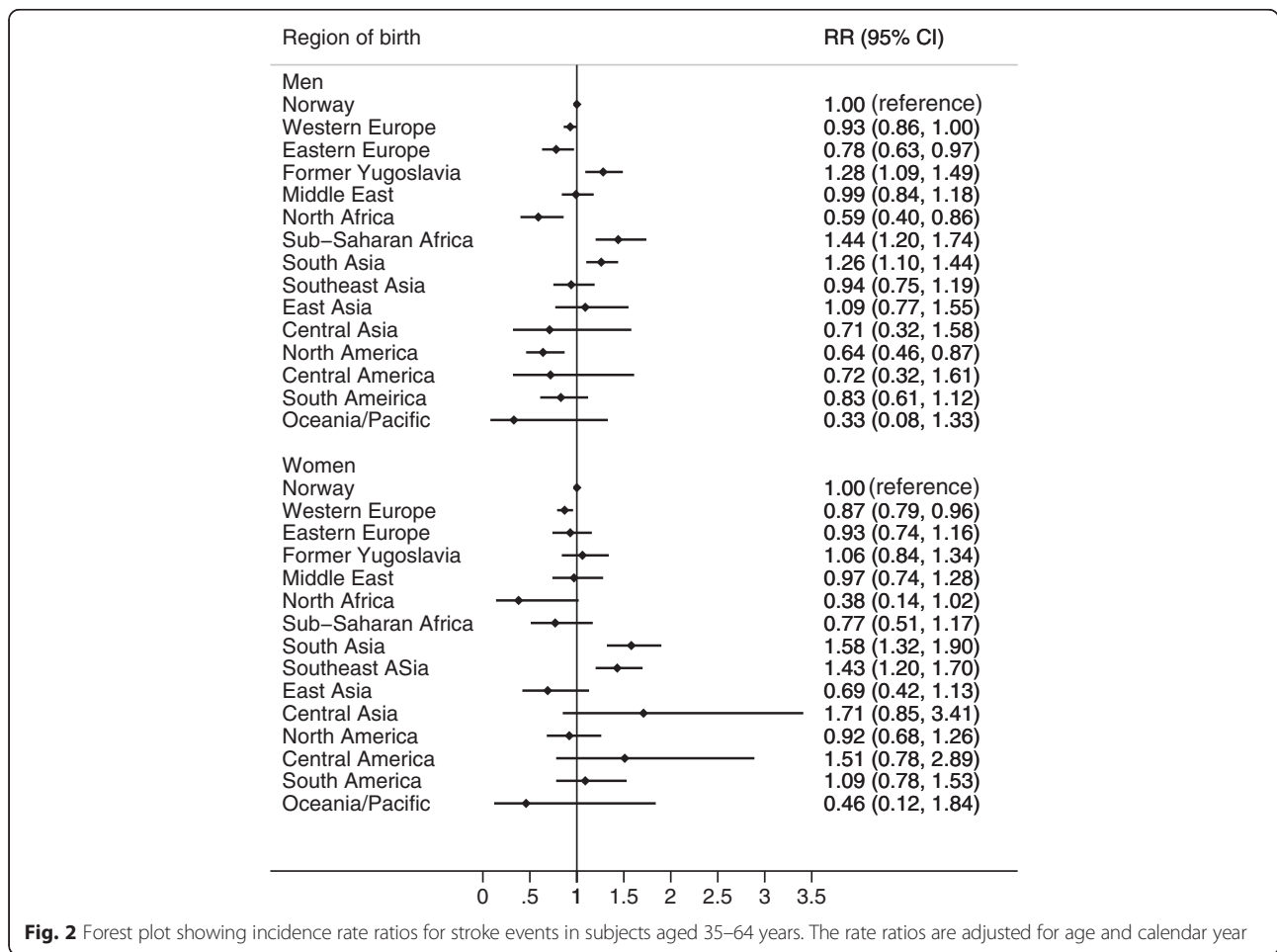
Page 6 of 10

Table 2 Age standardized stroke event rates per 100 000 person-years, subjects aged 35–64 years, CVDNOR 1994–2009

Country or region of birth	Men, *n* = 1 288 313			Women, *n* = 1 348 744		
	N	Strokes	SER (95 % CI)	N	Strokes	SER (95 % CI)
Norway	1 194 414	25528	194 (191–196)	1 160 158	15112	116 (115–118)
Western Europe	56 603	715	180 (166–193)	45 521	394	102 (92–112)
Denmark	10 581	186	206 (176–236)	9 474	103	109 (87–130)
Finland	3 248	74	340 (262–418)	3 889	49	155 (112–199)
Sweden	12 417	169	199 (169–229)	11 285	93	100 (80–120)
The Netherlands	2 938	27	159 (98–219)	2 221	12	72 (31–113)
Great Britain	9 955	107	145 (117–172)	5 511	48	95 (68–122)
Germany	8 339	81	161 (126–196)	6 552	45	88 (62–114)
Eastern Europe	23 031	86	157 (123–192)	14 550	76	110 (84–136)
Poland	15 698	36	145 (90–200)	5 599	43	148 (101–196)
Russia	1 429	6	177 (22–331)	4 188	15	77 (33–120)
Hungary	832	30	215 (131–299)	571	5	87 (9–165)
Former Yugoslavia	9 805	158	270 (227–313)	8 763	71	127 (96–157)
Bosnia-Hercegovina	4 437	78	231 (179–283)	4 470	52	151 (109–192)
Kosovo	2 790	24	275 (153–398)	2 130	11	188 (59–316)
Middle East	15 710	133	192 (154–230)	9 445	51	127 (88–165)
Turkey	3 651	42	211 (143–279)	2 377	13	76 (29–123)
Iraq	5 323	49	248 (163–332)	2 759	20	273 (141–404)
Iran	4 882	32	148 (87–209)	3 245	14	103 (47–159)
North Africa	4 078	26	125 (74–176)	1 803	4	32 (0–66)
Morocco	2 260	10	76 (26–126)	1 198	3	33 (0–74)
Sub-Saharan Africa	10 497	111	251 (197–304)	7 052	23	83 (44–122)
Somalia	3 583	49	464 (306–622)	2 490	7	84 (9–159)
South Asia	13 063	214	242 (208–276)	10 238	117	199 (161–238)
Sri Lanka	3 623	33	208 (116–299)	2 834	14	114 (45–182)
India	2 447	39	201 (137–265)	1 911	13	120 (52–188)
Pakistan	6 115	135	264 (219–309)	4 967	86	250 (194–306)
Southeast Asia	6 280	74	176 (134–218)	14 304	124	179 (144–214)
Philippines	1 227	16	180 (90–269)	4 642	43	171 (111–230)
Vietnam	4 303	48	167 (117–218)	4 161	46	183 (128–237)
East Asia	2 775	31	250 (162–339)	3 460	16	76 (38–115)
China	1 763	21	227 (130–324)	1 987	6	55 (9–100)
Central Asia	1 347	6	125 (18–232)	1 195	8	259 (75–442)
North America	5 812	39	122 (83–161)	5 867	40	110 (75–144)
USA	5 025	36	128 (85–170)	5 012	37	119 (80–158)
Central America	710	6	139 (27–250)	1 032	9	182 (53–310)
South America	3 870	42	182 (124–239)	4 342	34	115 (74–157)
Chile	2 472	34	206 (132–280)	1 999	15	104 (50–159)
Oceania/Pacific	749	2	60 (0–144)	583	2	55 (0–132)

SER standardized event rate, *CI* confidence interval

this region [27]. Moreover, most of the available studies are conducted in India and might not be generalizable for the whole region.

The increased risk of CVD in South Asians is not fully understood, but differences in metabolic risk factors have been found to account for some of their excess risk

Rabanal *et al. BMC Public Health* (2015) 15:1073

Page 7 of 10

Region of birth		RR (95% CI)
Men		
Norway		1.00 (reference)
Western Europe		0.93 (0.86, 1.00)
Eastern Europe		0.78 (0.63, 0.97)
Former Yugoslavia		1.28 (1.09, 1.49)
Middle East		0.99 (0.84, 1.18)
North Africa		0.59 (0.40, 0.86)
Sub–Saharan Africa		1.44 (1.20, 1.74)
South Asia		1.26 (1.10, 1.44)
Southeast Asia		0.94 (0.75, 1.19)
East Asia		1.09 (0.77, 1.55)
Central Asia		0.71 (0.32, 1.58)
North America		0.64 (0.46, 0.87)
Central America		0.72 (0.32, 1.61)
South Ameirica		0.83 (0.61, 1.12)
Oceania/Pacific		0.33 (0.08, 1.33)
Women		
Norway		1.00 (reference)
Western Europe		0.87 (0.79, 0.96)
Eastern Europe		0.93 (0.74, 1.16)
Former Yugoslavia		1.06 (0.84, 1.34)
Middle East		0.97 (0.74, 1.28)
North Africa		0.38 (0.14, 1.02)
Sub–Saharan Africa		0.77 (0.51, 1.17)
South Asia		1.58 (1.32, 1.90)
Southeast ASia		1.43 (1.20, 1.70)
East Asia		0.69 (0.42, 1.13)
Central Asia		1.71 (0.85, 3.41)
North America		0.92 (0.68, 1.26)
Central America		1.51 (0.78, 2.89)
South America		1.09 (0.78, 1.53)
Oceania/Pacific		0.46 (0.12, 1.84)

Fig. 2 Forest plot showing incidence rate ratios for stroke events in subjects aged 35–64 years. The rate ratios are adjusted for age and calendar year

[7, 10]. A recent prospective study from the UK found that waist-to-hip ratio was the individual risk factor that best attenuated the increased risk of CHD in South Asians compared to Europeans, although the risk remained significantly elevated also after adjustment (SHR 1.45, 95 % CI: 1.28–1.64) [7]. With regard to stroke, the same study found that diabetes was associated with a 2.5-fold age-adjusted incidence of stroke in South Asian immigrants.

Former Yugoslavia and Eastern Europe are two geographically close regions. Yet we found that immigrants from these two regions had very different risk of CVD. While immigrants from Former Yugoslavia had elevated risk of both AMI and stroke (the latter in men only) compared to ethnic Norwegians, the immigrants from Eastern Europe had similar or even reduced risk of both cardiovascular endpoints. This difference in risk might be related to differences in selection through migration. Concerning immigrants from Former Yugoslavia, increased risk of CVD could be related to traumatic war experiences prior to migration, since a great proportion of Former Yugoslavian immigrants came as refugees from the Balkan wars in the 1990's [28]. Posttraumatic stress disorder is associated with increased risk of CVD [29], and psychosocial factors

constitute an important risk factor for myocardial infarction and stroke [30, 31]. Immigrants from Eastern European countries are, to a greater extent, labor migrants and may therefore be a healthier group compared to the general population in their home countries. This would be in accordance with the "healthy immigrant effect" hypothesis [32]. Studies addressing the healthy immigrant phenomenon in Europe have, however, found mixed results [32, 33]. One of these studies grouped all immigrants into one group and compared them with the native populations of their host countries [33]. This has its limitations since different immigrant groups often vary in health, as demonstrated in the present study. Also, the healthy immigrant effect might not apply equally to all immigrant groups. The healthy immigrant effect is, for example, not evident in refugees [32]. In our study, lower risk was observed in immigrants from North America and Western Europe. This reduced risk could potentially, to some extent, be explained by the healthy immigrant effect since the reasons for migration for these groups are often related to work, family or education [34].

Another explanation for the healthy immigrant effect is the phenomenon of unhealthy remigration, also known as

Rabanal *et al. BMC Public Health* (2015) 15:1073

Page 8 of 10

the "salmon bias" [35]. The salmon bias refers to a compulsion to die in ones birthplace, and is expected to be more pronounced among older immigrants, since they often experience more health problems than the young. Although originally proposed for mortality data, the salmon effect is also relevant for morbidity data. Since we cannot rule out the possibility that immigrants in our study have experienced AMIs or strokes when visiting their home countries, the salmon effect could potentially contribute to an underestimation of AMI and stroke rates. The investigation of the salmon bias has, however, so far been scarce and the documentation of an existing effect is ambiguous [35–37]. A recent European study examining emigration from Denmark found, in fact, *lower* probability of emigration for immigrants with severe diseases [36].

The high risk of CVD found in immigrants from Former Yugoslavia is in accordance with high levels of cardiovascular risk factors previously reported in a Norwegian study for this group [16]. Studies from Sweden and Switzerland have also reported high levels of cardiovascular risk factors in Former Yugoslavian immigrants compared to the native populations, especially concerning overweight and obesity [38–40]. Available information on CVD mortality and morbidity in Former Yugoslavian countries also indicate high rates compared to Western European countries [41, 42]. Only a few studies have reported the incidence of AMI among immigrants from Former Yugoslavia settled in Western European countries, and the findings are somewhat inconclusive [6, 8, 43]. A case–control study from Austria reported increased risk of AMI in young (≤40 years) immigrants from Former Yugoslavia compared to native Austrians [43]. Meanwhile, a register-based study in Denmark did not find increased risk of CVD in this immigrant group compared to native Danes. The women from Former Yugoslavia did, however, have increased risk in some adjusted models [6]. All estimates in the Danish study were adjusted for marital status. In the present study, we have only adjusted for age and calendar year. Thus, a lack of social support indicated by marital status could possibly explain some of the discordance between the two studies. A more likely explanation, however, relates to the fact that the Danish study did not include war refugees. Consequently, the Former Yugoslavian group in the Danish study differed from our Former Yugoslavian group in a way that could have influence their risk of CVD.

As discussed, we found the highest risk of AMI in South Asians, and interestingly, the lowest risk was also observed in immigrants from Asia. Immigrants from East Asia had the lowest risk of AMI and Southeast Asians the second lowest risk. This concur with the literature reporting lower burdens of CHD in East Asian compared to Western populations, but not a lower burden of stroke [44]. The latter also confirmed in our study.

African Caribbean immigrants in the UK have reduced risk of CHD and increased risk of stroke compared to the European UK population [7]. We found decreased risk of AMI and increased risk of stroke in immigrant men from Sub-Sahara African countries concordant with UK findings.

In this study, we focused on a relatively young population regarding CVD risk. Consequently, our results concern the risk of getting CVD in an early age. In agreement with our findings, studies have found that South Asians acquire AMI in earlier ages than other ethnicities [30, 45]. Also, the previously mentioned study from Austria reporting increased risk of AMI in young immigrants from Former Yugoslavia [43] corresponds with this.

The mechanisms underlying ethnic differences in CVD are complex, and to explain the causes of the observed differences in CVD rates is beyond the scope of this paper. Numerous studies have tried to find explanations for the increased risk of CVD in South Asian populations, but so far, it is still not clear how much can be attributed to genetic and/or environmental factors [46]. Referring to the different stages of the epidemiologic transition, we know that CVD rates are dynamic and can be influenced by societal, demographic and environmental changes [47].

Strengths and limitations

This study has several strengths. First, the large sample size and national coverage make the findings relevant for the whole population in Norway in this age range. Also, the large sample size made it possible to analyse some countries of birth individually. This is a strength because of the heterogeneity in aggregated ethnic groups [48].

By using register data we minimize possible selection bias, although selection bias related to different use of health care services in immigrant groups [49] could possibly be present. We expect this to be limited, however, since we have focused on serious conditions and also included CVD deaths outside hospital. By updating the population at risk every year, we took possible emigration into account. Only immigrants with a valid personal ID were included in this study, thereby excluding individuals currently seeking asylum, tourists and some guest workers [50].

The AMI diagnosis in hospital discharge data in Norway have not been validated, but studies from Denmark and the Netherlands indicate a positive predictive value of about 90 % when AMI is coded as the main diagnosis [51–53]. Incident stroke discharge diagnosis was validated for a region in central Norway for the period 1994–1996 using a population-based stroke register as "gold-standard" [54]. The discharge data were found to overestimate the incidence of stroke, but the validity improved when restricting to acute stroke diagnoses. In the present study we have only used acute diagnoses for both endpoints and

Rabanal *et al. BMC Public Health* (2015) 15:1073

Page 9 of 10

have also made other restrictions to reduce possible over-estimation such as using the 28-day rule when defining events (see the methods section) and restricting the number of events per person. Also, since overdiagnosis and wrong coding of incident strokes happen more often when stroke is the secondary diagnosis [55], we excluded strokes coded as secondary diagnosis when the main diagnosis was rehabilitation. In a Danish study, AMI coded as secondary diagnosis had only slightly poorer validity, and the combination of National Hospital Registry data and National Death Registry data were found to be valid for monitoring CVD in the Danish population [53]. The validity of both the AMI and stroke diagnoses is unlikely to differ across the ethnic groups, and thus, it is unlikely that the validity of endpoints may have had any influence on the observed ethnic differences in CVD.

Conclusions

This study identified ethnic differences in risk of AMI and stroke in the Norwegian population aged 35–64 years. In particular, immigrants from South Asia and Former Yugoslavia had increased risk of AMI and stroke compared to ethnic Norwegians. Immigrants from North Africa, Western Europe, Eastern Europe and North America had similar or reduced risk compared to ethnic Norwegians.

This study has identified ethnic groups that should be targeted in future prevention efforts in order to reduce social health inequalities in Norway.

Additional file

Additional file 1: Table A1. Regions and countries of birth. Norwegian residents aged 35–64, 1994–2009. **Table A2.** Age standardized AMI event rates per 100 000 person-years, subjects aged 35–89 years, CVDNOR 1994–2009. **Table A3.** Age standardized stroke event rates per 100 000 person-years, subjects aged 35–89 years, CVDNOR 1994–2009. The additional tables provide supplementary information to the article. Table A1 lists all the countries within each region. Table A2 and A3 respectively show AMI and stroke event rates for a wider age group than the one we focused on in the article. (PDF 1020 kb)

Abbreviations

AF: Attributable fraction; AMI: Acute myocardial infarction; CHD: Coronary heart disease; CI: Confidence interval; CVD: Cardiovascular disease; CVDNOR: The cardiovascular disease in Norway project; ICD: International classification of diseases; RR: Rate ratio; UK: United Kingdom.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

GT established the CVDNOR project and obtained the data use for analyses. HM and GT were responsible for the conception of the current study. KR analysed the data and drafted the first paper. JI prepared the dataset and helped with the planning of statistical analyses. RS, JI, GT and HM contributed to the analyses of data and writing of the paper. All authors read and approved the final manuscript.

Author details

[1]Division of Epidemiology, Norwegian Institute of Public Health, P.O. Box 4404, Nydalen 0403 Oslo, Norway. [2]Department of Global Public Health and Primary Care, University of Bergen, P.O. Box 7804N-5018 Bergen, Norway. [3]Department of Health Registries, Norwegian Institute of Public Health, Kalfarveien 31, 5018 Bergen, Norway. [4]Department of Community Medicine, Institute of Health and Society, University of Oslo, P.O. Box 1130, Blindern 0318Oslo, Norway.

References

1. Albertinelli A, Knauth B, Kraszewska K, Thorogood D. Migrants in Europe: a statistical portrait of the first and second generation. Eurostat statistical books. Luxembourg: Publications Office of the European Union; 2011. ISBN 978-92-79-16231-2.
2. Rechel B, Mladovsky P, Ingleby D, Mackenbach JP, McKee M. Migration and health in an increasingly diverse Europe. Lancet. 2013;381(9873):1235–45.
3. Statistics Norway. Immigrants and Norwegian-born to immigrant parents, 1 January 2015. 2015. http://www.ssb.no/en/befolkning/statistikker/innvbef. Accessed 16 Oct 2015.
4. Gaziano TA, Bitton A, Anand S, Abrahams-Gessel S, Murphy A. Growing epidemic of coronary heart disease in low-and middle-income countries. Curr Probl Cardiol. 2010;35(2):72–115.
5. Wild SH, Fischbacher C, Brock A, Griffiths C, Bhopal R. Mortality from all causes and circulatory disease by country of birth in England and Wales 2001–2003. J Public Health (Oxf). 2007;29(2):191–8.
6. Hempler NF, Larsen FB, Nielsen SS, Diderichsen F, Andreasen AH, Jorgensen T. A registry-based follow-up study, comparing the incidence of cardiovascular disease in native Danes and immigrants born in Turkey, Pakistan and the former Yugoslavia: do social inequalities play a role? BMC Public Health. 2011;11:662.
7. Tillin T, Hughes AD, Mayet J, Whincup P, Sattar N, Forouhi NG, et al. The relationship between metabolic risk factors and incident cardiovascular disease in Europeans, south Asians, and African Caribbeans: SABRE (southall and Brent revisited)—A prospective population-based study. J Am Coll Cardiol. 2013;61(17):1777–86.
8. Hedlund E, Lange A, Hammar N. Acute myocardial infarction incidence in immigrants to Sweden. Country of birth, time since immigration, and time trends over 20 years. Eur J Epidemiol. 2007;22(8):493–503.
9. Lee J, Heng D, Chia KS, Chew SK, Tan BY, Hughes K. Risk factors and incident coronary heart disease in Chinese, Malay and Asian Indian males: the Singapore cardiovascular cohort study. Int J Epidemiol. 2001;30(5):983–8.
10. Anand SS, Yusuf S, Vuksan V, Devanesen S, Teo KK, Montague PA, et al. Differences in risk factors, atherosclerosis, and cardiovascular disease between ethnic groups in Canada: the Study of Health Assessment and Risk in Ethnic groups (SHARE). Lancet. 2000;356(9226):279–84.
11. Tillin T, Forouhi N, Johnston DG, McKeigue PM, Chaturvedi N, Godsland IF. Metabolic syndrome and coronary heart disease in South Asians, African-Caribbeans and white Europeans: a UK population-based cross-sectional study. Diabetologia. 2005;48(4):649–56.
12. Hjellset VT, Bjorge B, Eriksen HR, Hostmark AT. Risk factors for type 2 diabetes among female Pakistani immigrants: the InvaDiab-DEPLAN study on Pakistani immigrant women living in Oslo, Norway. J Immigr Minor Health. 2011;13(1):101–10.
13. Kumar B, Meyer H, Wandel M, Dalen I, Holmboe-Ottesen G. Ethnic differences in obesity among immigrants from developing countries, in Oslo, Norway. Int J Obes. 2006;30:684–90.
14. Yang D, Dzayee DA, Beiki O, de Faire U, Alfredsson L, Moradi T. Incidence and case fatality after day 28 of first time myocardial infarction in Sweden 1987–2008. Eur J Prev Cardiol. 2012;19(6):1304–15.

Rabanal *et al. BMC Public Health* (2015) 15:1073

Page 10 of 10

15. Bo A, Zinckernagel L, Krasnik A, Petersen JH, Norredam M. Coronary heart disease incidence among non-Western immigrants compared to Danish-born people: effect of country of birth, migrant status, and income. Eur J Prev Cardiol. 2014. doi:10.1177/2047487314551538.

16. Rabanal KS, Lindman AS, Selmer RM, Aamodt G. Ethnic differences in risk factors and total risk of cardiovascular disease based on the Norwegian CONOR study. Eur J Prev Cardiol. 2013;20(6):1013–21.

17. Igland J, Tell S, Ebbing M, Nygård O, Vollset S, Dimoski T. CVDNOR data and quality report: the CVDNOR project: cardiovascular disease in Norway 1994–2009. 2013. Description of data and data quality.

18. Sulo G, Igland J, Vollset SE, Nygård O, Øyen N, Tell GS. Cardiovascular disease and diabetes mellitus in Norway during 1994–2009. Nor Epidemiol. 2013;23(1):101–7.

19. Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJ, Lozano R, Inoue M. Age standardization of rates: a new WHO standard. Geneva: World Health Organization; 2001.

20. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. Philadelphia: Lippincott Williams & Wilkins; 2008.

21. Kumar B, Selmer R, Lindman A, Tverdal A, Falster K, Meyer H. Ethnic differences in SCORE cardiovascular risk in Oslo, Norway. Eur J Cardiovasc Prev Rehabil. 2009;16:229–34.

22. Glenday K, Kumar BN, Tverdal A, Meyer HE. Cardiovascular disease risk factors among five major ethnic groups in Oslo, Norway: the Oslo immigrant health study. Eur J Cardiovasc Prev Rehabil. 2006;13(3):348–55.

23. Fischbacher C, Bhopal R, Povey C, Steiner M, Chalmers J, Mueller G, et al. Record linked retrospective cohort study of 4.6 million people exploring ethnic variations in disease: myocardial infarction in South Asians. BMC Public Health. 2007;7(1):142.

24. McKeigue PM, Miller G, Marmot M. Coronary heart disease in south Asians overseas: a review. J Clin Epidemiol. 1989;42(7):597–609.

25. Bhopal R, Bansal N, Fischbacher C, Brown H, Capewell S. Ethnic variations in the incidence and mortality of stroke in the Scottish Health and Ethnicity Linkage Study of 4.65 million people. Eur J Prev Cardiol. 2012;19(6):1503–8.

26. Gill PS, Kai J, Bhopal RS, Wild S. Black and minority ethnic groups. In: Stevens A, Raftery J, Mant J, Simpson S, editors. Health care needs assessment: the epidemiologically based needs assessment reviews. Abingdon: Radcliffe Medical Press; 2007. p. 227–399.

27. Wasay M, Khatri IA, Kaul S. Stroke in South Asian countries. Nat Rev Neurol. 2014;10(3):135–43.

28. Henriksen K, Statistics Norway. Fakta om 18 innvandrergrupper i Norge. Reports 2007/29. 2007. Electronic version. ISBN 978-82-537-7222-6.

29. Wentworth BA, Stein MB, Redwine LS, Xue Y, Taub PR, Clopton P, et al. Post-traumatic stress disorder: a fast track to premature cardiovascular disease? Cardiol Rev. 2013;21(1):16–22.

30. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case–control study. Lancet. 2004;364(9438):937–52.

31. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case–control study. Lancet. 2010;376(9735):112–23.

32. Domnich A, Panatto D, Gasparini R, Amicizia D. The "healthy immigrant" effect: does it exist in Europe today? Ital J Public Health. 2012;9(3):e7532-1–7.

33. Moullan Y, Jusot F. Why is the 'healthy immigrant effect' different between European countries? Eur J Public Health. 2014;24 Suppl 1:80–6.

34. Høydahl E, editor. Innvandrere og norskfødte med innvandrerforeldre i 13 kommuner. 2014. (electronic): Statistics Norway. ISBN 978-82-537-8950-7.

35. Turra CM, Elo IT. The impact of salmon bias on the Hispanic mortality advantage: New evidence from social security data. Popul Res Policy Rev. 2008;27(5):515–30.

36. Norredam M, Hansen OH, Petersen JH, Kunst AE, Kristiansen M, Krasnik A, et al. Remigration of migrants with severe disease: myth or reality?-a register-based cohort study. Eur J Public Health. 2015;25(1):84–9.

37. Riosmena F, Wong R, Palloni A. Migration selection, protection, and acculturation in health: a binational perspective on older adults. Demography. 2013;50(3):1039–64.

38. Sundquist J, Cmelic-Eng M, Johansson SE. Body mass index and distribution of body fat in female Bosnian refugees—a study in primary health care. Public Health. 1999;113(2):89–93.

39. Marques-Vidal P, Vollenweider P, Waeber G, Paccaud F. Prevalence of overweight and obesity among migrants in Switzerland: association with country of origin. Public Health Nutr. 2011;14(7):1148–56.

40. Grossmann FF, Leventhal ME, Auer-Boer B, Wanner P, Bischoff A. Self-reported cardiovascular risk factors in immigrants and Swiss nationals. Public Health Nurs. 2011;28(2):129–39.

41. Nichols M, Townsend N, Luengo-Fernandez R, Leal J, Gray A, Scarborough P, et al. European cardiovascular disease statistics 2012. Sophia Antipolis: European Heart Network, Brussels, European Society of Cardiology; 2012.

42. Dilic M. Current data for CVD in Bosnia and Herzegovina and experience with Our Own guidelines. J Am Coll Cardiol. 2013;62(18_S2):C203.

43. Wiesbauer F, Blessberger H, Goliasch G, Holy EW, Pfaffenberger S, Tentzeris I, et al. Elevated risk of myocardial infarction in very young immigrants from former Yugoslavia. Eur J Epidemiol. 2009;24(11):691–6.

44. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: Part II: variations in cardiovascular disease by specific ethnic groups and geographic regions and prevention strategies. Circulation. 2001;104(23):2855–64.

45. Gholap N, Davies M, Patel K, Sattar N, Khunti K. Type 2 diabetes and cardiovascular disease in South Asians. Prim Care Diabetes. 2011;5(1):45–56.

46. Zaman MJ, Bhopal RS. New answers to three questions on the epidemic of coronary mortality in south Asians: incidence or case fatality? Biology or environment? Will the next generation be affected? Heart. 2013;99(3):154–8.

47. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. Circulation. 2001;104(22):2746–53.

48. Bhopal R. Race and ethnicity: responsible use from epidemiological and public health perspectives. J Law Med Ethics. 2006;34(3):500–7.

49. Diaz E, Calderon-Larranaga A, Prado-Torres A, Poblador-Plou B, Gimeno-Feliu LA. How do immigrants use primary health care services? A register-based study in Norway. Eur J Public Health. 2015;25(1):72–8.

50. Nystadnes T. Identifikatorer for personer, syntaks for fødselsnummer, hjelpenummer mv. Versjon 1.0. KITH-standard 1001:2010 kompetansesenter for IT i helsevesenet AS. 2010.

51. Joensen AM, Jensen MK, Overvad K, Dethlefsen C, Schmidt E, Rasmussen L, et al. Predictive values of acute coronary syndrome discharge diagnoses differed in the Danish national patient registry. J Clin Epidemiol. 2009;62(2):188–94.

52. Merry AH, Boer JA, Schouten L, Feskens EJM, Verschuren WMM, Gorgels APM, et al. Validity of coronary heart diseases and heart failure based on hospital discharge and mortality data in the Netherlands using the cardiovascular registry Maastricht cohort study. Eur J Epidemiol. 2009;24(5):237–47.

53. Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M. The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. J Clin Epidemiol. 2003;56(2):124–30.

54. Ellekjaer H, Holmen J, Kruger O, Terent A. Identification of incident stroke in Norway: hospital discharge data compared with a population-based stroke register. Stroke. 1999;30(1):56–60.

55. Indredavik B, Fjærtoft H, Ellekjær H, Skogseth-Stephani R, Mørch B. Norsk hjerneslagregister. Årsrapport 2013. Plan for forbedringstiltak. Nasjonalt sekretariat for Norsk hjerneslagregister, Seksjon for medisinske kvalitetsregistre. St. Olavs Hospital. 01.10.2014. Available at:www.norskhjerneslagregister.no . Accessed 16 Oct 2015.

Table A1 Regions and countries of birth. Norwegian residents aged 35-64, 1994-2009

Regions	Countries
Norway (n=2 354 572)	Norway
Western Europe (n=102 124)	Denmark (n=20 055), Greenland (n=168), Finland (n=7 137), Fareo islands (n=795), Sweden (n=23 702), Belgium (n=757), Andorra (n=4), France (n=2 972), Gibraltar (n=7), Greece (n=686), Ireland (n=569), Italy (n=1 640), Malta (n=48), Netherlands (n=5 159), Liechtenstein (n=12), Luxembourg (n=29), Monaco (n=4), Portugal (n=631), San Marino (n=4), Spain (n=1 607), Great Briatin (n=15 466), Switzerland (n=1 031), Germany (n=14 891), Austria (n=936), Israel (n=451), Cyprus (n=106), Iceland (n=3 257)
Eastern Europe (n=37 581)	Estonia (n=636), Bulgaria (n=1 066), Belarus (n=267), Latvia (n=711), Poland (n=21 297), Romania (n=1 403), Lithuania (n=2 456), Moldavia (n=110), Russia (n=5 617), Ukraine (n=844), Hungary (n=1 403), Slovakia (n=853), Georgia (n=105), Czech Republic (n=813)
Former Yugoslavia (n=18 568)	Albania (n=142), Croatia (n=1 693), Slovenia (n=111), Bosnia-Hercegovina (n=8 907), Macedonia (n=1 296), Serbia (n=1 325), Montenegro (n=174), Kosovo (n=4 920)
Middle East (n=25 155)	Turkey (n=6 028), Armenia (n=99), Aserbadsjan (n=142), Bahrain (n=8), The United Arab Emirates (n=11), Iraq (n=8 082), Iran (n=8 127), Jordan (n=113), Kuwait (n=102), Lebanon (n=1 075), Palestine (n=639), Qatar (n=3), Saudi Arabia (n=35), Syria (n=636), Yemen (n=52), Oman (n=3)
North Africa (n=5 881)	Tunisia (n=604), Algeria (n=823), Egypt (n=475), Libya (n=91), Morocco (n=3 458), Sudan (n=362), Southern Sudan(n=68)
Sub-Saharan Africa (n=17 549)	Angola (n=149), Botswana (n=37), Equatorial Guinea (n=3), Ivory Coast (n=116), Eritrea (n=1 644), Ethiopia (n=1 733), Djibouti (n=8), Gambia (n=767), Ghana (n=1 072), Guinea (n=39), Guinea-Bissau (n=10), Cameroon (n=165), Cape Verde (n=350), Congo (n=520), Liberia (n=267), Madagascar (n=168), Mauritania (n=11) Mauritius (n=154), Namibia (n=50) Nigeria (n=518), Mozambique (n=83), Zimbabwe (n=132), Rwanda (n=182), São Tomé and Príncipe (n=1), Senegal (n=73), Central African Republic (n=2), Sierra Leone (n=208), Somalia (n=6 073), South Africa (n=649), Burundi (n=221), Comoros (n=4), Benin (n=8), Gabon (n=7), Congo-Brazzaville (n=46), Kenya (n=586), Lesotho (n=4), Malawi (n=59), Mali (n=23), West-Sahara (n=4), Niger (n=12), Réunion (n=6), Seychelles (n=11), Swaziland (n=6), Chad (n=15), Togo (n=55), Tanzania (n=611), Uganda (n=496), Zambia (n=171), Burkina Faso (n=20)
South Asia (n=23 301)	Bangladesh (n=395), Bhutan (n=13), Myanmar (n=740), Sri Lanka (n=6 457), India (n=4 358), Nepal (n=256), Pakistan (n=11 082)
Southeast Asia (n=20 584)	Brunei (n=4), Phillipines (n=5 869), Indonesia (n=477), Cambodia (n=165), Laos (n=46) Malaysia (n=326), East-Timor (n=5), Singapore (n=275), Thailand (n=4 953), Vietnam (n=8 464)
East Asia (n=6 235)	Taiwan (n=137), Hongkong (n=665), Japan (n=879), China (n=3 750), North-Korea (n=18), South-Korea (n=698), Mongolia (n=24), Macao (n=64)
Central Asia (n=2 542)	Afghanistan (n=1980), Kasakhstan (n=351), Tadsjikistan (n=29), Turkmenistan(n=25), Kirgisistan(n=45), Uzbekistan (n=112)
North America (n=11 679)	Canada (n=1 642), USA (n=10 037)
Central America (n=1 742)	Cayman Islands (n=2), Costa Rica (n=62), Cuba (n=335), Dominica (n=9), the Dominican Republic (n=190), Grenada (n=14), Guadeloupe (n=4), Haiti (n=13), Honduras (n=54), Jamaica (n=91), Martinique (n=9) Mexico (n=397), Aruba (n=19), Curacao (n=42), Nicaragua (n=64), Panama (n=27), El Salvador (n=75), Saint Lucia (n=3), Saint Vincent and Grenadine (n=2), Trinidad and Tobago (n=272), American Virgin Islands (n=2), British Virgin Islands (n=1), Barbados (n=17), Antigua and Barbuda (n=2), Belize (n=8), Bahamas (n=7), Bermuda (n=5), Puerto Rico (n=16)
South America (n=8 212)	Guatemala (n=89), Argentina (n=483), Bolivia (n=132), Brazil (n=1 138), Guyana (n=74), Chile (n=4 471), Columbia (n=619), Ecuador (n=166), French Guyana (n=1), Paraguay (n=45), Peru (n=519), Surinam (n=23), Uruguay (n=160), Venezuela (n=292)
Oceania/Pacific (n=1 332)	American Samoa (n=1), Australia (n=931), Salomon Islands (n=2), Cook islands (n=4), Fiji (n=24), French Polynesia (n=3), Tonga (n=5) Tuvalu (n=1), New Zealand (n=346), Federated states of Micronesia (n=1), Samoa (n=2), New Caledonia (n=6), Papua New Guinea(n=5), Palau (n=1)

Table A2 Age standardized AMI event rates per 100 000 person-years for subjects aged 35-89 years, CVDNOR 1994-2009

Country or region of birth	Men 35-89 years, n=1 634 520			Women 35-89 years, n=1 682 539		
	N	AMIs	SER (95 % CI)	N	AMIs	SER (95 % CI)
Norway	1 472 970	156129	992 (987-997)	1 542 459	95142	441 (438-444)
Western Europe	*59 931*	*2768*	*1009 (965-1054)*	*51 919*	*1486*	*367 (348-385)*
Denmark	11 830	986	1156 (1073-1239)	11 004	403	363 (326-400)
Finland	3 384	174	1397 (1125-1669)	4 148	70	337 (252-422)
Sweden	13 191	526	937 (843-1031)	13 139	384	380 (342-419)
The Netherlands	3 062	104	1052 (785-1320)	2 416	37	283 (187-379)
Great Britain	10 268	340	824 (700-948)	6 591	245	395 (345-444)
Germany	8 664	300	908 (781-1035)	7 390	198	370 (318-423)
Eastern Europe	*23 801*	*545*	*1216 (1102-1329)*	*15 324*	*154*	*371 (309-433)*
Poland	16 083	252	1243 (1067-1418)	5 804	51	316 (217-415)
Russia	1 499	36	1181 (783-1579)	4 396	23	374 (217-530)
Hungary	938	115	1079 (831-1326)	675	39	541 (360-722)
Former Yugoslavia	*10 370*	*556*	*1167 (1019-1316)*	*9 582*	*269*	*702 (603-801)*
Bosnia-Hercegovina	4 852	326	1087 (919-1255)	5 055	179	684 (565-804)
Kosovo	2 838	91	1290 (646-1933)	2 226	37	971 (578-1364)
Middle East	*15 952*	*501*	*1026 (840-1211)*	*9 788*	*99*	*542 (389-694)*
Turkey	3 684	142	715 (552-877)	2 425	40	736 (405-1067)
Iraq	5 384	139	1229 (849-1609)	2 844	22	493 (215-771)
Iran	5 008	165	991 (714-1268)	3 427	30	510 (234-786)
North Africa	*4 122*	*73*	*630 (354-907)*	*1 847*	*9*	*136 (31-241)*
Morocco	2 277	43	590 (252-927)	1 223	5	116 (00-236)
Sub-Saharan Africa	*10 641*	*161*	*636 (444-828)*	*7 301*	*34*	*247 (150-343)*
Somalia	3 623	60	851 (324-1378)	2 575	9	170 (57-284)
South Asia	*13 491*	*916*	*1327 (1169-1485)*	*10 829*	*210*	*619 (511-727)*
Sri Lanka	3 760	135	1329 (786-1873)	3 045	25	453 (226-680)
India	2 560	131	895 (679-1111)	2 075	51	649 (461-838)
Pakistan	6 283	633	1533 (1306-1761)	5 171	131	646 (477-815)
Southeast Asia	*6 467*	*155*	*564 (436-692)*	*14 596*	*75*	*312 (223-402)*
Philippines	1 258	32	288 (183-393)	4 725	11	53 (13-93)
Vietnam	4 433	100	528 (383-673)	4 337	40	291 (191-391)
East Asia	*2 975*	*63*	*672 (493-852)*	*3 724*	*29*	*225 (140-311)*
China	1 949	51	679 (485-874)	2 216	18	196 (105-286)
Central-Asia	*1 382*	*39*	*1285 (344-2226)*	*1 235*	*12*	*668 (42-1294)*
North America	*6 976*	*377*	*768 (691-846)*	*7 746*	*336*	*355 (315-394)*
USA	6 089	351	791 (709-874)	6 724	288	331 (292-371)
Central-America	*731*	*19*	*927 (346-1508)*	*1 058*	*6*	*101 (15-187)*
South-America	*3 942*	*113*	*916 (594-1238)*	*4 495*	*45*	*292 (192-393)*
Chile	*2 500*	*76*	*476 (278-673)*	*2 071*	*18*	*216 (87-346)*
Oseania/Pacific	*769*	*15*	*1236 (511-1961)*	*636*	*6*	*164 (28-300)*

AMI: Acute Myocardial Infarction; SER: Standardized event rate; CI: Confidence Interval

Table A3 Age standardized stroke event rates per 100 000 person-years for subjects aged 35-89 years, CVDNOR 1994-2009

Country or region of birth	Men 35-89 years, n=1 634 520			Women 35-89 years, n=1 682 539		
	N	Strokes	SER (95 % CI)	N	Strokes	SER (95 % CI)
Norway	1 472 970	114072	744 (739-748)	1 542 459	109861	509 (506-512)
Western Europe	*59 931*	*1858*	*763 (723-804)*	*51 919*	*1990*	*495 (473-517)*
Denmark	11 830	696	846 (774-919)	11 004	535	492 (449-536)
Finland	3 384	125	847 (650-1043)	4 148	122	545 (439-651)
Sweden	13 191	356	727 (641-813)	13 139	510	501 (458-545)
The Netherlands	3 062	73	743 (524-962)	2 416	44	334 (230-438)
Great Britain	10 268	196	641 (520-762)	6 591	299	488 (433-543)
Germany	8 664	220	883 (748-1018)	7 390	266	505 (444-567)
Eastern Europe	*23 801*	*350*	*872 (773-971)*	*15 324*	*224*	*492 (423-562)*
Poland	16 083	159	924 (767-1081)	5 804	82	442 (330-553)
Russia	1 499	13	404 (172-636)	4 396	44	526 (350-702)
Hungary	938	82	952 (681-1223)	675	41	600 (404-796)
Former Yugoslavia	*10 370*	*290*	*725 (607-844)*	*9 582*	*249*	*653 (558-749)*
Bosnia-Hercegovina	4 852	182	711 (572-850)	5 055	179	666 (550-781)
Kosovo	2 838	29	867 (123-1610)	2 226	26	661 (372-951)
Middle East	*15 952*	*191*	*679 (493-865)*	*9 788*	*93*	*449 (320-578)*
Turkey	3 684	59	440 (263-617)	2 425	23	555 (233-876)
Iraq	5 384	65	676 (387-965)	2 844	37	566 (363-769)
Iran	5 008	52	682 (377-987)	3 427	27	351 (156-545)
North Africa	*4 122*	*40*	*437 (167-708)*	*1 847*	*17*	*465 (209-721)*
Morocco	2 277	15	114 (51-177)	1 223	10	347 (97-597)
Sub-Saharan Africa	*10 641*	*158*	*760 (542-977)*	*7 301*	*55*	*404 (273-534)*
Somalia	3 623	64	885 (566-1204)	2 575	13	201 (61-342)
South Asia	*13 491*	*295*	*655 (515-796)*	*10 829*	*200*	*628 (512-744)*
Sri Lanka	3 760	41	403 (200-606)	3 045	29	413 (216-610)
India	2 560	61	677 (405-948)	2 075	39	547 (364-731)
Pakistan	6 283	186	682 (494-870)	5 171	127	736 (542-929)
Southeast-Asia	*6 467*	*159*	*696 (550-841)*	*14 596*	*208*	*593 (480-706)*
Philippines	1 258	21	522 (62-983)	4 725	50	244 (139-348)
Vietnam	4 433	120	709 (547-870)	4 337	115	647 (510-784)
East Asia	*2 975*	*74*	*703 (530-876)*	*3 724*	*72*	*526 (398-654)*
China	1 949	59	700 (513-888)	2 216	47	488 (348-628)
Central-Asia	*1 382*	*8*	*308 (2-614)*	*1 235*	*15*	*1132 (234-2030)*
North-America	*6 976*	*317*	*643 (573-713)*	*7 746*	*427*	*478 (430-525)*
USA	6 089	285	638 (564-711)	6 724	381	479 (428-530)
Central-America	*731*	*18*	*886 (353-1419)*	*1 058*	*12*	*369 (81-657)*
South-America	*3 942*	*60*	*691 (376-1005)*	*4 495*	*69*	*472 (339-605)*
Chile	*2 500*	40	443 (94-791)	*2 071*	26	361 (184-539)
Oseania/Pacific	*769*	*7*	*633 (92-1174)*	*636*	*8*	*227 (68-387)*

SER: Standardized event rate; CI: Confidence Interval

BMJ Open

Can traditional risk factors explain the higher risk of cardiovascular disease in South Asians compared to Europeans in Norway and New Zealand? Two cohort studies

Kjersti S Rabanal,[1] Haakon E Meyer,[1,2] Grethe S Tell,[3,4] Jannicke Igland,[4] Romana Pylypchuk,[5] Suneela Mehta,[5] Bernadette Kumar,[6] Anne Karen Jenum,[7] Randi M Selmer,[1] Rod Jackson[5]

For numbered affiliations see end of article.

Correspondence to
Kjersti S Rabanal;
kjersti.stormark.rabanal@fhi.no

ABSTRACT

Objectives The objective was to prospectively examine potential differences in the risk of first cardiovascular disease (CVD) events between South Asians and Europeans living in Norway and New Zealand, and to investigate whether traditional risk factors could explain any differences.

Methods We included participants (30–74 years) without prior CVD in a Norwegian (n=16 606) and a New Zealand (n=129 449) cohort. Ethnicity and cardiovascular risk factor information was linked with hospital registry data and cause of death registries to identify subsequent CVD events. We used Cox proportional hazards regression to investigate the relationship between risk factors and subsequent CVD for South Asians and Europeans, and to calculate age-adjusted HRs for CVD in South Asians versus Europeans in the two cohorts separately. We sequentially added the major CVD risk factors (blood pressure, lipids, diabetes and smoking) to study their explanatory role in observed ethnic CVD risk differences.

Results South Asians had higher total cholesterol (TC)/high-density lipoprotein (HDL) ratio and more diabetes at baseline than Europeans, but lower blood pressure and smoking levels. South Asians had increased age-adjusted risk of CVD compared with Europeans (87%–92% higher in the Norwegian cohort and 42%–75% higher in the New Zealand cohort) and remained with significantly increased risk after adjusting for all major CVD risk factors. Adjusted HRs for South Asians versus Europeans in the Norwegian cohort were 1.57 (95% CI 1.19 to 2.07) in men and 1.76 (95% CI 1.09 to 2.82) in women. Corresponding figures for the New Zealand cohort were 1.64 (95% CI 1.43 to 1.88) in men and 1.39 (95% CI 1.11 to 1.73) in women.

Conclusion Differences in TC/HDL ratio and diabetes appear to explain some of the excess risk of CVD in South Asians compared with Europeans. Preventing dyslipidaemia and diabetes in South Asians may therefore help reduce their excess risk of CVD.

Strengths and limitations of this study

► This is one of few prospective investigations of cardiovascular disease and its risk factors in South Asian populations living in Western countries.
► A special feature is the inclusion of prospective data from two different countries enhancing the external validity of the findings.
► The two cohorts differed in how participants were recruited and how information about risk factor levels was collected at baseline.
► A limited number of South Asians in the Norwegian cohort and short follow-up time in the New Zealand cohort restricted the statistical power in our analyses.

Sri Lanka and Bangladesh) who have settled in Western countries have increased risk of cardiovascular disease (CVD) compared with their host populations of European origin.[1] This excess risk has been documented in several countries, especially the increased risk of coronary heart disease (CHD).[2–4] We recently found that South Asian immigrants in Norway had more than twofold higher risk of acute myocardial infarction (AMI) than ethnic Norwegians and an increased risk of stroke (26% higher in men and 58% higher in women).[5] Collaborators in New Zealand found a higher risk of CVD in Indians compared with the European New Zealand population.[6]

The mechanisms underlying the increased risk of CVD in South Asian populations are to a great extent unknown.[1] Few studies have examined the prospective relationship between CVD risk factors and subsequent CVD among South Asians,[4 7–9] despite the urgent need for such studies being addressed

INTRODUCTION

Immigrants from South Asia (countries in the Indian subcontinent, such as India, Pakistan,

for more than 10 years ago.[10] The two large and multinational case–control studies, INTERHEART[11] and INTERSTROKE,[12] indicate that different populations share the same risk factors and that the relationship between risk factors and CVD is similar in different populations around the world. The INTERHEART study also concluded that the earlier age of AMI in South Asians can be largely attributed to higher risk-factor levels at younger ages.[13] However, the INTERHEART and INTERSTROKE studies are both case–control studies. In both Norway and New Zealand, South Asians have been found to have similar or higher mean total cholesterol (TC) to high-density lipoprotein (HDL) ratio and higher prevalence of diabetes compared with the European majority populations.[14–17] However, they also have lower levels of smoking (especially women) and mean systolic blood pressure (SBP) than the European majority populations. Whether the higher risk of CVD among South Asians in Norway and New Zealand is due to higher levels of certain risk factors have not previously been studied.

Due to the dearth of prospective data on the relationship between risk factors and CVD among South Asians, we aimed to prospectively examine possible differences in the risk of a first CVD event between South Asians and Europeans using cohort studies from Norway and New Zealand, and to examine whether traditional CVD risk factors could explain such differences. Since the two cohorts differ in several aspects we do not intend to compare the two cohorts directly, but mainly focus on within-country comparisons.

MATERIAL AND METHODS
The New Zealand PREDICT-CVD cohort
We used data from the PREDICT-CVD cohort, collected through use of the PREDICT web-based decision support program in New Zealand for the assessment and management of CVD risk during primary healthcare consultations.[18] The study methods and data definitions are described in detail elsewhere.[18 19] In short, the software has been integrated with commonly used primary care management systems, and allows systematically coded CVD risk data to be automatically and anonymously extracted from patients' electronic medical records and augmented where required by primary care staff.[18 19] The cardiovascular profile data was subsequently linked, using an encrypted national health identifier number to national and regional health datasets with information about hospitalisations, deaths, publicly funded drug dispensing and laboratory test claims and results.[19]

The PREDICT software is used in around 35% of New Zealand primary care practices mainly in the Auckland and Northland regions,[19] which serve around 1.7 million people, representing around 37% of the New Zealand population.[20] Any patient with their CVD risk assessed by a general practitioner (GP) or practice nurse into online PREDICT-CVD forms are included in the PREDICT cohort.

New Zealand CVD risk management guidelines recommend that all men aged over 45 years and all women aged over 55 years have a regular CVD risk assessment.[21] Specified high-CVD risk groups, including those of South Asian ethnicity, are recommended to undergo a risk assessment 10 years earlier than the general population.

We used PREDICT data from August 2002 to September 2012. Members of the cohort were enrolled and examined continuously throughout this period via their contact with the primary healthcare. We included individuals aged 30–74 years since the dataset comprised people undergoing a risk assessment based on a Framingham risk score intended for people in this age group.[22] Using information from the GP, hospital discharges and medication dispensing, we excluded persons with a history of CVD (CHD (including angina), stroke, transient ischaemic attack (TIA), peripheral vascular disease, percutaneous coronary intervention or coronary artery bypass grafting), or atrial fibrillation at baseline (n=24 537), and people with overt renal disease, those who had estimated glomerular filtration rate ≤29 and those with prior hospitalisations for congestive heart failure (HF) or who were on loop diuretics at baseline (n=1582). Only subjects with European or Indian background were included. The risk factor measurements in the PREDICT cohort were extracted from a standardised electronic template that primary care practitioners completed. The SBP was based on the mean of the last two recordings done by the GP or practice nurse, in most cases with a manual mercury sphygmomanometer. Blood lipid and glucose or glycated haemoglobin measurements were carried out in the community laboratories routinely used by GPs and smoking status and other risk factor data were measured using a standard questionnaire completed by a primary care practitioner.

Cohort of Norway
We included participants from three surveys conducted during 2000 to 2002 in Oslo, Norway; The Oslo Health Study (HUBRO), The Oslo Immigrant Health Study (I-HUBRO) and The Romsås in Motion study (MoRo II) (n=26 709), which are part of the Cohort of Norway (CONOR)[23]; a collection of health data and blood samples from several Norwegian health surveys. Participation rates for the three studies were 40%–46%.[23]

All CONOR surveys followed the same standard procedure for collection of data from self-administered questionnaires, physical measurements and blood samples. The CONOR questionnaire provided information on self-reported diabetes, smoking, use of blood pressure (BP) and/or lipid-lowering medication and family history of CVD. All participants attended a clinical examination and non-fasting venous blood samples were drawn. SBP was measured by an automatic device (DINAMAP, Criticon, Tampa, FL, USA) after 2 min of seated resting. Three recordings were made at 1-min intervals. For the analyses we used the average of the second and third SBP measurements. The blood

samples were subsequently measured for TC and HDL cholesterol.[23]

Using an 11-digit personal identifier, CONOR data were linked to hospitalisations and deaths in the Cardiovascular Disease in Norway (CVDNOR) project, 1994 to 2009.[24 25] This enabled us to follow CONOR participants for CVD outcomes (hospitalisations or deaths) occurring after CONOR examination through 31 December 2009.

We included participants aged 30–74 years at baseline (n=3871 excluded) to ensure comparable samples between the Norwegian and New Zealand data. We excluded participants not born in Norway or South Asia (n=5651 excluded), pregnant women (n=197), and participants with prior CVD (CHD, cerebrovascular disease, atherosclerotic disease, TIA and HF) (n=353) or atrial fibrillation (n=31) registered in the hospital data before screening.

Outcomes

In both cohorts, we identified the first CVD event (non-fatal and fatal) using main or secondary diagnoses from hospital discharge data or the underlying cause of death from national mortality statistics. The International Classification of Diseases (ICD) codes (versions 9 and/or 10) were used to define outcome variables. New Zealand hospitals used an Australian modification of the ICD-10 classification called ICD10-AM.[26]

CVD in both cohorts included the following conditions: CHD; HF; cerebrovascular disease including TIA; diseases of arteries, arterioles and capillaries including atherosclerosis, aneurysm and dissection as well as embolism and thrombosis. For the Norwegian cohort, this included the codes: ICD9: 410–414, 428, 430–438, 440, 441 except 441.7, 442, 443.9, 444; ICD10: I20–I25, I50, I60–I69, I70–I79, G45. The CVD variable in the New Zealand PREDICT cohort included the same ICD10 codes as just listed, and also some additional ICD10-codes (I469, J81, G460–G468, Z951, Z955, Z958, Z959) plus a list of procedure codes (too many to be listed here). The PREDICT-CVD outcome has been described elsewhere.[19]

Ethnicity

Ethnicity in the New Zealand PREDICT data was based on two sources: (1) the PREDICT template filled in by the GP and (2) the National Health Index dataset, both according to pre-defined categories. A prioritising algorithm was used to agree on one ethnicity in case of multiple ethnicities recorded (details can be found in the online supplementary file entitled the VIEW Ethnicity Protocol). The system for coding ethnicity in New Zealand enables identification of Indian people, who account for approximately 90% of South Asian people living in New Zealand. The remaining South Asian ethnic groups are classified as part of the 'Other Asian' ethnic group in national health data and so could not be included here. Indian people can include both immigrants and individuals who have been born in New Zealand with parents (or older generations) who have immigrated. The majority of this group

are immigrants since 76.5% of the people who identified themselves with the Indian ethnic group in New Zealand in 2013 were born overseas.[27]

For the Norwegian cohort, we used country of birth merged into larger world regions to define ethnicity.[28] We defined South Asians as individuals who migrated to Norway from Bangladesh, Myanmar, Sri Lanka, Pakistan, India or Nepal.[28] The largest share of South Asians in this dataset (95%) came from the HUBRO or the I-HUBRO study. HUBRO and I-HUBRO combined included 1145 Sri Lankans and 780 Pakistanis,[29] indicating that about 50% of the South Asian group (n=2206) in the present study are Sri Lankans and 35% are Pakistanis.

In general, we refer to the ethnic groups as South Asians (South Asians in Norway and/or Indians in New Zealand) and Europeans (ethnic Norwegians and/or New Zealanders with ethnic European origin). Most European New Zealanders are of British and Irish ancestry, of whom about three-quarters were born in New Zealand.

Statistical analysis

Baseline characteristics are reported as mean values with SD for continuous variables and fractions for categorical variables. We tested the differences between the ethnic groups adjusted for age by analysis of covariance. We used Cox regression models to examine the prospective relationship between baseline risk factors (BP, lipids, diabetes and smoking) and time until subsequent first CVD event. People were censored if they died from other causes (n=961 in PREDICT and n=276 in CONOR). Cox regression was also used to calculate HRs for CVD in South Asians versus Europeans using ethnicity as the exposure variable and adjusting for risk factors. The order we added the risk factors to the model was based on the distribution of risk factors in the subpopulations. This meant that we first introduced the risk factors that were more prevalent among South Asians compared with Europeans (diabetes and TC/HDL ratio) and then added the two less prevalent risk factors (SBP and smoking). Additional analyses where we added the risk factors in different orders and looked at each risk factor in separate models with only age as covariate did not change the conclusions (Tables A1 and A2 in the online supplementary appendix). Proportional hazards assumptions were tested using scaled Schoenfeld residuals.[30] All analyses were stratified by sex and ethnicity, except for the analyses where ethnicity was the exposure variable in which we only stratified by sex. Only complete cases were included in the analyses. Stata V.14 was used for analyses in the Norwegian data and Stata V.11 for analysis in the New Zealand data.

To check whether the use of BP medication at baseline would impact the analyses where SBP were included, we repeated the Cox regression analyses excluding people using antihypertensive medication at baseline. Correspondingly, we also repeated the Cox regression analyses for TC/HDL ratio without people using lipid-lowering medication at baseline. In addition, since excluding those

at highest risk could potentially impact the sensitivity analyses, we also adjusted for medication use without excluding anyone from the analyses (Tables A3 and A4 in the online supplementary appendix).

Ethics

The current project was approved by the Regional Committee for Medical Research Ethics, Health Region West. The PREDICT study was approved by the Northern Region Ethics Committee Y in 2003 (AKY/03/12/134), and later annually approved by the National Multi Region Ethics Committee since 2007 (MEC07/19/EXP).[19] Each individual CONOR study was approved by the Norwegian Data Inspectorate and evaluated by the Regional Committee for Medical Research Ethics.[31] Both datasets contained anonymised data.

RESULTS

Baseline characteristics

The final study sample from the New Zealand cohort consisted of 129 449 individuals (43% women) of European (87%) or Indian ethnicity (13%) with no history of CVD, atrial fibrillation or renal disease. Correspondingly for the Norwegian cohort, the final study sample consisted of 16 606 individuals (54% women) born in either Norway (87%) or South Asia (13%) with no history of CVD or atrial fibrillation.

At baseline, the Norwegian cohort was younger than the New Zealand cohort, and New Zealand women were older than New Zealand men (table 1). In both cohorts, South Asians were younger than Europeans.

South Asians had lower levels of TC and HDL and higher mean levels of TC/HDL ratios than Europeans in both Norway and New Zealand. South Asians also had the lowest SBP levels (table 1). These differences persisted after adjustment for age (P<0.05 for differences between ethnic groups—results not shown).

The diabetes baseline prevalence was higher among South Asians compared with Europeans in both cohorts (table 1). The difference in diabetes were the same after adjustment for age (P<0.001). Antihypertensive and lipid-lowering treatments were generally more prevalent among South Asians than Europeans, and more prevalent in the New Zealand cohort compared with the Norwegian cohort. Cigarette smoking was more common among Europeans than South Asians, and practically none of the South Asian women smoked. Mean follow-up time was significantly longer in the Norwegian cohort than in the New Zealand cohort (table 1).

CVD events

During follow-up, we observed 2654 CVD events among 129 449 individuals in the New Zealand cohort (378 874 person-years) and 743 new CVD events among the 16 606 individuals in the Norwegian cohort (139 470 person-years). The overall crude rates were 700 per 100 000 person-years in the New Zealand cohort and 533 per 100

000 person-years in the Norwegian cohort. Ethnic specific rates for men and women in the two cohorts are shown in table 2 and in Tables A5–A8 of the online supplementary appendix. Also crude rates and age-adjusted HRs of CVD by risk factors, ethnic groups, cohort and gender can be found in the same tables (online supplementary appendix).

Prospective associations between risk factors and CVD

Increasing age was significantly associated with risk of CVD in both ethnic groups in both cohorts (table 2). The age effect was very similar within the countries for both ethnic groups and gender, but was stronger in the Norwegian cohort compared with the New Zealand cohort. After adjustment for age, the traditional CVD risk factors were positively associated with CVD in both ethnic groups, across gender and country. Whereas all the risk factor–CVD event associations were statistically significant in Europeans, the 95% CIs were wider and the results not always statistically significant among South Asians. The relationship between SBP, TC/HDL ratio, smoking and subsequent CVD appeared to be weaker in Indian men compared with European men in the New Zealand cohort. The prospective association between the risk factors and CVD changed little after adjusting for the other risk factors in addition to age (results not shown). In the sensitivity analyses where we either adjusted for medication use (Table A3 in the Appendices) or excluded people using BP- and lipid lowering medication at baseline (results not shown), the estimates for the prospective associations between risk factors and CVD were similar as in the main analyses. However, for women in the New Zealand cohort, after excluding people on lipid-lowering medication, the HR for TC/HDL ratio changed to 1.12 (95% CI 0.91 to 1.39) for Indian women and to 1.20 (95% CI 1.12 to 1.27) for European women.

Ethnic difference in CVD

South Asians of both genders in Norway and New Zealand had increased risk of CVD compared with the European majority populations (table 3), with age-adjusted HRs ranging from 1.42 to 1.92. After adjustment for TC/HDL ratio and diabetes, the HRs for South Asians versus Europeans were reduced and no longer significant in women. Additional adjustments for SBP and smoking increased the HRs again so that South Asians in both countries had significantly increased risk of CVD compared with Europeans. After adjustment for age, TC/HDL ratio, diabetes, SBP and smoking, the HRs for the excess risk in South Asians compared with Europeans varied from 1.39 to 1.76. The largest reduction in risk estimate after full adjustment was seen in South Asian men in the Norwegian cohort where the HR was lowered by approximately 38% after adjusting for the four major risk factors. The smallest reduction in risk estimate after adjustment was among South Asian women in the New Zealand cohort where the risk estimate was only reduced by 7% (from 1.42 to 1.39).

Table 1 Baseline characteristics (unadjusted) of the Norwegian and New Zealand participants. Participants free of prior CVD.

	Men		Women	
	European	Indian	European	Indian
New Zealand cohort				
N	63 319	9997	49 094	7039
Age (years)	55.0 (9.3)	47.4 (9.7)	58.7 (8.7)	52.9 (8.5)
Age range	30.0–74.0	30.0–74.0	30.0–74.0	30.0–74.0
TC (mmol/L)	5.36 (1.1)	5.09 (1.1)	5.68 (1.1)	5.04 (1.0)
HDL cholesterol (mmol/L)	1.29 (0.4)	1.14 (0.3)	1.59 (0.5)	1.30 (0.3)
LDL cholesterol (mmol/L)	3.3 (1.0)	2.9 (1.0)	3.4 (1.1)	2.8 (0.9)
TC/HDL ratio	4.35 (1.3)	4.60 (1.3)	3.68 (1.1)	3.93 (1.1)
SBP (mm Hg)	131.5 (16.3)	125.3 (16.1)	131.6 (17.4)	126.1 (17.4)
Diastolic blood pressure (mm Hg)	80.5 (10.0)	79.1 (10.4)	78.8 (9.7)	77.4 (9.8)
Hypertension* (%)	40	34	44	39
Type 2 diabetes† (%)	9	24	9	29
Former smokers (%)	19	6	16	1
Current smokers (%)	12	9	10	1
Family history of CVD‡ (%)	12	8	15	10
Antihypertensive treatment (%)	24	26	30	32
Lipid-lowering treatment (%)	18	27	18	27
Follow-up time (years)	2.94 (2.3)	2.93 (2.0)	2.92 (2.3)	2.83 (1.9)
	Men		Women	
	Norwegian	South Asian	Norwegian	South Asian
Norwegian cohort				
N	6385	1 239	8015	967
Age (years)	43.7 (11.2)	41.4 (7.8)	43.9 (10.9)	40.3 (7.9)
Age range	30.0–70.1	30.0–67.8	30.0–74.9	30.0–65.5
TC (mmol/L)	5.60 (1.1)	5.48 (1.0)	5.41 (1.0)	4.98 (0.9)
HDL cholesterol (mmol/L)	1.31 (0.3)	1.07 (0.2)	1.62 (0.4)	1.24 (0.3)
TC/HDL ratio	4.55 (1.4)	5.33 (1.4)	3.52 (1.1)	4.22 (1.2)
SBP (mm Hg)	132.6 (14.4)	126.6 (13.2)	124.0 (15.7)	119.1 (15.6)
Diastolic blood pressure (mm Hg)	77.6 (10.8)	76.9 (9.8)	71.5 (10.3)	70.0 (10.1)
Hypertension* (%)	30	22	19	16
Diabetes (%)	1.6	8.6	1.4	10.9
Former smokers (%)	28	16	26	2
Current smokers (%)	26	25	31	1
Family history of heart disease§ (%)	33	24	37	27
Family history of stroke¶ (%)	11	3	13	4
Antihypertensive treatment (%)	6	8	6	9
Lipid-lowering treatment (%)	4	6	3	6
Follow-up time (years)	8.44 (1.4)	7.65 (1.4)	8.54 (1.2)	7.88 (1.1)

*Hypertension is defined as having SBP ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or using blood pressure medication.
†The diabetes variable in the New Zealand data includes people with diabetes of unknown type (5%) and type 2 diabetes (95%), while in the Norwegian data we could not differentiate between different types of diabetes.
‡Family history of CVD in the New Zealand data: self-reported familial history of ischaemic heart disease or ischaemic stroke occurring in a father or brother aged <55 years, or a mother or sister aged <65 years.
§Parents or siblings have had heart attack or angina pectoris (self-report).
¶Parents or siblings have had stroke (self-report).
Data are mean values (SD) for continuous variables and prevalence (%) for categorical variables.
CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure, TC, total cholesterol.

Table 2 Age-adjusted HRs for first CVD event after baseline for selected risk factors in men and women aged 30–74 years with no history of CVD, stratified by cohort, ethnicity and gender

	N events/N*	Crude rate/100 000 person-years (95% CI)	Age (1 year) HR (95% CI)	SBP (10mm Hg) HR (95% CI)	DBP (10mm Hg) HR (95% CI)	TC/HDL ratio (one unit) HR (95% CI)	Diabetes (yes/no) HR (95% CI)	Current smoking (yes/no) HR (95% CI)
New Zealand cohort								
European men	1518/63 319	815 (775 to 857)	1.07 (1.06 to 1.07)	1.15 (1.12 to 1.18)	1.16 (1.10 to 1.22)	1.20 (1.16 to 1.23)	1.92 (1.68 to 2.19)	2.29 (2.02 to 2.59)
Indian men	273/9997	933 (828 to 1050)	1.06 (1.05 to 1.07)	1.05 (0.98 to 1.13)	1.02 (0.91 to 1.14)	1.08 (0.98 to 1.19)	1.72 (1.34 to 2.20)	1.45 (0.99 to 2.11)
Norwegian cohort								
Norwegian men	379/6385	703 (636 to 778)	1.10 (1.09 to 1.11)	1.15 (1.08 to 1.22)	1.19 (1.08 to 1.30)	1.22 (1.15 to 1.30)	3.15 (2.14 to 4.65)	1.86 (1.51 to 2.29)
South Asian men	79/1239	833 (668 to 1039)	1.11 (1.08 to 1.14)	1.17 (1.01 to 1.35)	1.21 (0.97 to 1.51)	1.23 (1.05 to 1.42)	1.61 (0.90 to 2.86)	1.43 (0.88 to 2.30)
New Zealand cohort								
European women	757/49 094	528 (492 to 567)	1.06 (1.05 to 1.07)	1.09 (1.05 to 1.13)	1.13 (1.05 to 1.22)	1.14 (1.09 to 1.21)	1.93 (1.59 to 2.35)	2.74 (2.30 to 3.27)
Indian women	106/7039	531 (439 to 643)	1.06 (1.03 to 1.08)	1.27 (1.16 to 1.39)	1.25 (1.03 to 1.50)	1.21 (1.03 to 1.41)	2.29 (1.55 to 3.37)	2.60 (0.64 to 10.59)
Norwegian cohort								
Norwegian women	259/8015	378 (335 to 427)	1.10 (1.09 to 1.12)	1.20 (1.12 to 1.28)	1.32 (1.18 to 1.47)	1.30 (1.19 to 1.43)	2.79 (1.52 to 5.11)	2.22 (1.73 to 2.84)
South Asian women	26/967	341 (232 to 501)	1.14 (1.09 to 1.19)	1.06 (0.86 to 1.30)	1.07 (0.74 to 1.55)	1.04 (0.77 to 1.39)	2.74 (1.21 to 6.22)	†

*The numbers of events and people included in the analyses may differ due to missing risk factor data. Few were missing in the NZ cohort.
†Not calculated due to no exposed cases.
CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol.

Open Access

Table 3 HRs (95% CI) for first CVD event in South Asian groups compared with ethnic European groups in New Zealand and Norway

	Men		Women	
	Indian NZ versus European NZ	South Asians versus Norwegians	Indian NZ versus European NZ	South Asians versus Norwegians
N events/N	1791/73 308	436/7387	863/56 126	264/8558
Adjusted for				
Age	1.75 (1.53 to 2.00)	1.92 (1.48 to 2.49)	1.42 (1.16 to 1.75)	1.87 (1.21 to 2.87)
Age, TC/HDL ratio	1.77 (1.55 to 2.02)	1.66 (1.27 to 2.16)	1.41 (1.14 to 1.73)	1.52 (0.98 to 2.36)
Age, TC/HDL ratio, diabetes	1.49 (1.30 to 1.71)	1.42 (1.08 to 1.87)	1.15 (0.92 to 1.42)	1.30 (0.82 to 2.04)
Age, TC/HDL ratio, diabetes, SBP	1.57 (1.37 to 1.80)	1.53 (1.16 to 2.01)	1.19 (0.96 to 1.47)	1.31 (0.83 to 2.07)
Age, TC/HDL ratio, diabetes, SBP, smoking	1.64 (1.43 to 1.88)	1.57 (1.19 to 2.07)	1.39 (1.11 to 1.73)	1.76 (1.09 to 2.82)

All had complete information on the risk factors.
CVD, cardiovascular disease; HDL, high-density lipoprotein; NZ, New Zealand; SBP, systolic blood pressure; TC, Total cholesterol.

Additional analyses showed that the excess risk in South Asians was particularly high for CHD. The full-adjusted HRs for CHD (corresponding to the analyses in the last row of table 3) were 2.07 (95% CI 1.76 to 2.44) in South Asian men and 1.60 (95% CI 1.20 to 2.13) in South Asian women in New Zealand. In the Norwegian cohort, the full-adjusted HRs for CHD were 1.86 (95% CI 1.36 to 2.55) in South Asian men and 2.84 (95% CI 1.61 to 5.03) in South Asian women (Table A9 in the Appendices). In the sensitivity analyses for table 3 where we excluded people using BP-lowering or lipid-lowering medication at baseline (results not shown) or adjusted for BP-lowering or lipid-lowering medication (Table A4 in the Appendices), the patterns according to the risk factor adjustments remained the same as in the main analysis.

DISCUSSION

This study confirmed that the traditional risk factors SBP, TC/HDL ratio, diabetes and smoking are all positively associated with risk of CVD in South Asians as well as in Europeans. The present study also confirmed that South Asians had an increased risk of CVD compared with Europeans and that ethnic differences in the distribution of TC/HDL ratio and type 2 diabetes appear to explain some of this excess risk.

The main strengths of this study are the prospective study design, and inclusion of data from two countries. Unfortunately, we lacked information about duration of stay for the immigrants, and the ethnic groups that we studied are heterogeneous.

Strengths of the PREDICT cohort are the large sample size and the completeness of risk factors included in the risk-assessment. Only 0.01% were missing on any of the four major risk factors because they were part of the prediction algorithm and thereby compulsory to fill in to the PREDICT template. Furthermore, comprehensive national health registers were used to identify and exclude people with prior CVD and to determine

cardiovascular outcomes. In the New Zealand cohort, some recruitment bias is likely since risk assessment was initially prioritised for high-risk patients. Indian patients are therefore over-represented in the cohort together with Maoris and Pacifics.[19] The representativeness of the source population is, however, improving as PREDICTs coverage increases. In this study, follow-up extended to 2012 when PREDICT included 50% of guideline-eligible patients in the practices where the PREDICT software is used.[19] We did not assume that the cohorts were representative of the general populations in the two countries, but that the ethnic groups within the two cohorts should be comparable. Adjusting for age was therefore particularly important in the New Zealand cohort since South Asians were around 7 years younger than Europeans. Results from the two cohorts showed approximately the same regarding ethnic differences, which is a strength concerning the external validity of these results. A limitation in the New Zealand data is short follow-up time restricting the statistical power. Another limitation is the lack of standardised BP measurements since recorded BP can easily be affected by a range of factors including the type of device used.[32]

Strengths of CONOR data are the standardised measurements of risk factors, the linkage with disease outcomes from comprehensive national health registers and the standardised way of defining ethnicity using country of birth. A validation study examining the Oslo Health study, showed that participants with a non-Western background had a lower participation rate than others.[33] This may reflect self-selection, which can work both ways; healthy and resourceful people have the energy and motivation to participate or less healthy people who think their health could benefit from participating do so. Self-selection is unlikely to influence associations between risk factors and subsequent disease, but could influence the ethnic comparisons if the mechanisms were systematically different for the ethnic groups. The South Asian

group in the Norwegian cohort was relatively small, which reduced the precision of the estimates and limited the statistical power. Another limitation in the CONOR data is missing information on some of the risk factors (see Tables A5-A8 in the Appendices for numbers of missing). However, the extent of missing was small. The risk factor with most missing in CONOR was diabetes (3% for the total cohort).

In both cohorts, the endpoints are based on register data, including both hospital and mortality data, which enables almost complete ascertainment of CVD events. In New Zealand, more than 95% of patients with an acute CVD event are managed by government-funded health services.[19] However, CVD events occurring among participants who travelled outside of New Zealand, those who emigrated after the index CVD risk assessment or among participants treated in private hospitals would not be captured in the national hospital and mortality registers.[19] We have no information about possible emigration for the New Zealand cohort, but for the Norwegian cohort we know that few people have emigrated (about 1% of the ethnic Norwegians and <3% of the South Asians who participated in the Oslo health studies had emigrated by the end of follow-up). A limitation for both cohorts is also the lack of medication data during follow-up. However, adjustment for baseline medication did not change the estimates (Tables A3-A4 in the Appendices), and table 1 shows that South Asians used more antihypertensives and lipid-lowering drugs at baseline than Europeans. Both countries have universal healthcare and South Asians should have the same access to cardiovascular medication as Europeans. It is therefore not likely that lack of treatment explains the differences in risk of CVD between the two ethnic groups.

Our finding that the traditional major CVD risk factors contribute to the development of CVD in South Asians as in Europeans was an expected, yet important, finding since most knowledge about CVD prevention is based on studies in populations of European descent, and some have questioned whether these risk factors apply worldwide.[11 34] This finding is in line with the large INTER-HEART and INTERSTROKE case–control studies,[11 12] which reported that 90% of the population attributable risk for AMI and stroke worldwide was accounted for by, respectively, nine and ten (similar) risk factors, including those included in the present study. We are only aware of two other prospective studies reporting HRs for the prospective relationship between major CVD risk factors and subsequent CVD in South Asians.[7 35] One of these studies included only men,[7] and the other showed estimates for men and women combined and did not include blood lipids.[35] These studies generally agree with our findings that traditional risk factors contribute to the development of CVD in South Asians as in Europeans.[7 35] Also, consistent with previous reports,[5 6] we found that South Asians in both Norway and New Zealand have a higher risk of CVD compared with the European majority populations. By including all the measured risk factors

(BP, TC/HDL ratio, diabetes and smoking) as adjustment variables in one statistical model, we could not explain the higher risk of CVD in South Asians. However, the increased risk was attenuated when we only included the risk factors more prevalent in South Asians than in Europeans (TC/HDL ratio and diabetes).

The excess risk of CVD among South Asians compared with Europeans in the Norwegian cohort was almost two-fold. This is comparable to what we reported previously when studying the total Norwegian population.[5] The South Asians in the New Zealand cohort had 42%–75% higher risk of CVD compared with European New Zealanders, which also agrees with previous New Zealand studies.[6] In both the Norwegian and New Zealand data, South Asians had higher baseline levels of dyslipidaemia indicated by the TC/HDL ratio and higher diabetes prevalence compared with the European majority populations, which is in general agreement with previous knowledge from these countries.[14–16] Attenuation of the excess risk in South Asians versus Europeans was best achieved in the Cox model only including diabetes and TC/HDL ratio as covariates in addition to age. The same was found in both cohorts, clearly indicating that the unfavourable distribution of blood lipids and type 2 diabetes explains some of the higher risk of CVD in South Asians. South Asians generally have a high prevalence of metabolic risk factors related to insulin resistance, often clustered so that they match the concept of the metabolic syndrome.[36–39] A British cohort study that tested whether traditional risk factors could account for the high mortality of CHD among South Asian men compared with European men, reported that adjusting for insulin resistance, dyslipidaemia and hyperglycaemia in South Asians did not explain their higher risk.[7] However, they also adjusted for smoking and TC, which were both less prevalent/lower among South Asian men compared with European men.

It is unclear why the traditional risk factors do not completely explain the excess risk of CVD in South Asians. This could be related to incomplete adjustments; due to either imprecise measurement of risk factors or that other important risk factors were not included (eg, waist measurement, length of time since diabetes diagnosis). A number of non-conventional risk factors are also thought to partially account for the high risk of CVD in South Asians, including dysfunctional HDL, C reactive protein, thrombogenic risk factors, telomere length, high homocysteine levels and low birth weight.[40 41] Socioeconomic factors could probably also explain some of the differences in risk between the ethnic groups, but we did not have such variables. Another possibility is that risk factors work cumulatively over time in the development of atherosclerosis, and some risk factors may also work at specific and crucial time points during the life course. Measurements taken on single occasions may also lead to an underestimation of the strength between the usual levels of the risk factors and later disease, known as the regression dilution bias.[42] Consequently, it is unlikely

Open Access

that the ethnic differences would disappear completely by adjusting for selected risk factors measured once in midlife.

Although South Asians seem to have an underlying susceptibility for metabolic diseases, traditional and modifiable risk factors are important for preventing disease. Our analyses indicate that it is important to focus on the prevention of type 2 diabetes and dyslipidaemia when aiming to reduce the burden of CVD among South Asians. The additional effect of abdominal obesity for the risk of CVD among South Asians in Norway and New Zealand has, however, not yet been studied although we know that the prevalence is high in this ethnic group.[37 43] In both Norway[44 45] and New Zealand,[46] intervention studies targeting immigrants from South Asia have been carried out with some promising results. A UK study that prospectively examined the influence from four health behaviours on the risk of CVD in South Asian immigrants and UK Europeans found an important potential for disease prevention among South Asians if they adhered to healthy behaviours.[8]

CONCLUSION

Ethnic differences in distribution of TC/HDL ratio and type 2 diabetes explained some, but not all, of the excess risks of CVD in South Asians compared with Europeans in Norway and New Zealand. Smoking and elevated BP were less prevalent among South Asians and thus could not explain any of the observed differences in risk of CVD. Targeted diabetes and dyslipidaemia management among South Asians, including support for healthy lifestyle choices, should be a priority if the high burden of CVD in these ethnic populations is to be reduced.

Author affiliations
[1]Division for Mental and Physical Health, Norwegian Institute of Public Health, Oslo, Norway
[2]Department of Community Medicine, Institute of Health and Society, University of Oslo, Oslo, Norway
[3]Division for Health Data and Digitalisation, Norwegian Institute of Public Health, Bergen, Norway
[4]Department of Global Public Health and Primary Care, University of Bergen, Norway
[5]School of Population Health, University of Auckland, Auckland, New Zealand
[6]Norwegian Center for Minority Health Research, Oslo, Norway
[7]Faculty of Health and Society, Institute of Health and Society, University of Oslo, Oslo, Norway

REFERENCES

1. Zaman MJ, Bhopal RS. New answers to three questions on the epidemic of coronary mortality in south Asians: incidence or case fatality? Biology or environment? Will the next generation be affected? *Heart* 2013;99:154–8.
2. Bo A, Zinckernagel L, Krasnik A, et al. Coronary heart disease incidence among non-Western immigrants compared to Danish-born people: effect of country of birth, migrant status, and income. *Eur J Prev Cardiol* 2015;22:1281–9.
3. Hedlund E, Lange A, Hammar N. Acute myocardial infarction incidence in immigrants to Sweden. Country of birth, time since immigration, and time trends over 20 years. *Eur J Epidemiol* 2007;22:493–503.
4. Tillin T, Hughes AD, Mayet J, et al. The relationship between metabolic risk factors and incident cardiovascular disease in Europeans, South Asians, and African Caribbeans: SABRE (Southall and Brent Revisited) -- a prospective population-based study. *J Am Coll Cardiol* 2013;61:1777–86.
5. Rabanal KS, Selmer RM, Igland J, et al. Ethnic inequalities in acute myocardial infarction and stroke rates in Norway 1994-2009: a nationwide cohort study (CVDNOR). *BMC Public Health* 2015;15:1073.
6. Ministry of Health. *Asian Health Chart Book 2006*. Wellington: Ministry of Health, 2006.
7. Forouhi NG, Sattar N, Tillin T, et al. Do known risk factors explain the higher coronary heart disease mortality in South Asian compared with European men? Prospective follow-up of the Southall and Brent studies, UK. *Diabetologia* 2006;49:2580–8.
8. Eriksen A, Tillin T, O'Connor L, et al. The impact of health behaviours on incident cardiovascular disease in Europeans and South Asians–a prospective analysis in the UK SABRE study. *PLoS one* 2015;1:15.
9. de Munter JS, Agyemang C, Stronks K, et al. Association of physical activity, smoking, and alcohol intake with CVD-related hospital discharge in people of European, South Asian, or African descent. *Eur J Prev Cardiol* 2013;20:80–8.
10. Ranganathan M, Bhopal R. Exclusion and inclusion of nonwhite ethnic minority groups in 72 North American and European cardiovascular cohort studies. *PLoS Med* 2006;3:e44.
11. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:937–52.
12. O'Donnell MJ, Xavier D, Liu L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 2010;376:112–23.
13. Joshi P, Islam S, Pais P, et al. Risk factors for early myocardial infarction in South Asians compared with individuals in other countries. *JAMA* 2007;297:286–94.
14. Perumal L, Wells S, Ameratunga S, et al. Markedly different clustering of CVD risk factors in New Zealand Indian and European people but similar risk scores (PREDICT-14). *Aust N Z J Public Health* 2012;36:141–4.
15. Jenum AK, Diep LM, Holmboe-Ottesen G, et al. Diabetes susceptibility in ethnic minority groups from Turkey, Vietnam, Sri Lanka and Pakistan compared with Norwegians - the association

with adiposity is strongest for ethnic minority women. *BMC Public Health* 2012;12:150.

16. Rabanal KS, Lindman AS, Selmer RM, *et al*. Ethnic differences in risk factors and total risk of cardiovascular disease based on the Norwegian CONOR study. *Eur J Prev Cardiol* 2013;20:1013–21.

17. Kumar BN, Selmer R, Lindman AS, *et al*. Ethnic differences in SCORE cardiovascular risk in Oslo, Norway. *Eur J Cardiovasc Prev Rehabil* 2009;16:229–34.

18. Bannink L, Wells S, Broad J, *et al*. Web-based assessment of cardiovascular disease risk in routine primary care practice in New Zealand: the first 18,000 patients (PREDICT CVD-1). *N Z Med J* 2006;119:U2313.

19. Wells S, Riddell T, Kerr A, *et al*. Cohort Profile: The PREDICT Cardiovascular Disease Cohort in New Zealand Primary Care (PREDICT-CVD 19). *Int J Epidemiol* 2015:dyv312. dyv312.

20. Statistics New Zealand. *Subnational population estimates tables*. Wellington: Statistics New Zealand, 2014.

21. New Zealand Guideline Group. *The assessment and Management of Cardiovascular Risk. 2003*. Wellington, New Zealand.

22. Anderson KM, Odell PM, Wilson PW, *et al*. Cardiovascular disease risk profiles. *Am Heart J* 1991;121:293–8.

23. Naess O, Søgaard AJ, Arnesen E, *et al*. Cohort profile: cohort of Norway (CONOR). *Int J Epidemiol* 2008;37:481–5.

24. Sulo G, Igland J, Vollset SE, *et al*. Cardiovascular disease and diabetes mellitus in Norway during 1994-2009 CVDNOR – a nationwide research project. *Nor Epidemiol* 2013;23.

25. Sulo G, Igland J, Nygård O, *et al*. Favourable trends in incidence of AMI in Norway during 2001–2009 do not include younger adults: a CVDNOR project. *Eur J Prev Cardiol* 2014;21:1358–64.

26. Ministry of Health. Wellington. ICD-10-AM/ACHI/ACS: Ministry of Health, 2015. Retrieved 25 Sep 2015 from http://www.health.govt.nz/nz-health-statistics/classification-and-terminology/icd-10-am-achi-acs.

27. Statistics New Zealand. Tatauranga Aotearoa. 2013 Census. Ethnic group profile: Indian. Retrieved 11 Sep 2015 from http://www.stats.govt.nz/Census/2013-census/profile-and-summary-reports/ethnic-profiles.aspx?request_value=24743&parent_id=24726&tabname=# 2013.

28. Norwegian Institute of Public Health. Documentation of the CONOR file. Version 02.07.2012. Retrieved 14 Dec 2016 from https://www.fhi.no/globalassets/migrering/dokumenter/pdf/documentation-of-the-conor-file.pdf.

29. Kumar B, Grøtvedt L, Meyer H, *et al*. *The Oslo immigrant health profile, in Rapport 2008:7*. Oslo: Norwegian Institute of Public Health, 2008.

30. Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika* 1982;69:239–41.

31. Sogaard A. Cohort Norway (CONOR): Materials and methods: Norwegian Institute of Public Health. 2007 http://www.fhi.no/studier/cohort-of-norway.

32. Tolonen H, Koponen P, Naska A, *et al*. Challenges in standardization of blood pressure measurement at the population level. *BMC Med Res Methodol* 2015;15:33.

33. Søgaard AJ, Selmer R, Bjertness E, *et al*. The Oslo Health Study: The impact of self-selection in a large, population-based survey. *Int J Equity Health* 2004;3:1–12.

34. Pais P, Pogue J, Gerstein H, *et al*. Risk factors for acute myocardial infarction in Indians: a case-control study. *Lancet* 1996;348:358–63.

35. Williams ED, Stamatakis E, Chandola T, *et al*. Physical activity behaviour and coronary heart disease mortality among South Asian people in the UK: an observational longitudinal study. *Heart* 2011;97:655–9.

36. Alberti KG, Eckel RH, Grundy SM, *et al*. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009;120:1640–5.

37. Misra A, Khurana L. The metabolic syndrome in South Asians: epidemiology, determinants, and prevention. *Metab Syndr Relat Disord* 2009;7:497–514.

38. McKeigue PM, Shah B, Marmot MG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. *Lancet* 1991;337:382–6.

39. Hjellset VT, Bjørge B, Eriksen HR, *et al*. Risk factors for type 2 diabetes among female Pakistani immigrants: the InvaDiab-DEPLAN study on Pakistani immigrant women living in Oslo, Norway. *J Immigr Minor Health* 2011;13:101–10.

40. Ahmed E, El-Menyar A. South Asian ethnicity and cardiovascular risk: the known, the unknown, and the paradox. *Angiology* 2015;66:405–15.

41. Nair M, Prabhakaran D. Why Do South Asians Have High Risk for CAD? *Glob Heart* 2012;7:307–14.

42. MacMahon S, Peto R, Cutler J, *et al*. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;335:765–74.

43. Kumar BN, Meyer HE, Wandel M, *et al*. Ethnic differences in obesity among immigrants from developing countries, in Oslo, Norway. *Int J Obes* 2006;30:684–90.

44. Telle-Hjellset V, Råberg Kjøllesdal MK, Bjørge B, *et al*. The InnvaDiab-DE-PLAN study: a randomised controlled trial with a culturally adapted education programme improved the risk profile for type 2 diabetes in Pakistani immigrant women. *Br J Nutr* 2013;109:529–38.

45. Andersen E, Høstmark AT, Holme I, *et al*. Intervention effects on physical activity and insulin levels in men of Pakistani origin living in Oslo: a randomised controlled trial. *J Immigr Minor Health* 2013;15:101–10.

46. Rush EC, Chandu V, Plank LD. Reduction of abdominal fat and chronic disease factors by lifestyle change in migrant Asian Indians older than 50 years. *Asia Pac J Clin Nutr* 2007;16:671–6.

BMJ Open

Can traditional risk factors explain the higher risk of cardiovascular disease in South Asians compared to Europeans in Norway and New Zealand? Two cohort studies

Kjersti S Rabanal, Haakon E Meyer, Grethe S Tell, Jannicke Igland, Romana Pylypchuk, Suneela Mehta, Bernadette Kumar, Anne Karen Jenum, Randi M Selmer and Rod Jackson

Updated information and services can be found at:

http://bmjopen.bmj.com/content/7/12/e016819

These include:

References	This article cites 36 articles, 4 of which you can access for free at: **http://bmjopen.bmj.com/content/7/12/e016819#BIBL**
Open Access	This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/
Email alerting service	Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections	Articles on similar topics can be found in the following collections Epidemiology (2218)

Notes

Appendix

Table A1. Hazard ratios (95% CI) for first CVD event in South Asian groups compared to ethnic European groups in New Zealand and Norway- risk factors introduced in a different order than in the main analyses.

	Men		Women	
	Indian vs. European NZ	South Asians vs. Norwegians	Indian NZ vs. European NZ	South Asians vs. Norwegians
N events/N	1791/73308	436/7387	863/56126	264/8558
Adjusted for				
Age	1.75 (1.53-2.00)	1.92 (1.48-2.49)	1.42 (1.16-1.75)	1.87 (1.21-2.87)
Age, diabetes	1.48 (1.29-1.70)	1.64 (1.25-2.15)	1.15 (0.93-1.43)	1.52 (0.96-2.39)
Age, diabetes, SBP	1.56 (1.36-1.79)	1.76 (1.34-2.31)	1.19 (0.96-1.48)	1.49 (0.94-2.36)
Age, diabetes, SBP, smoking	1.63 (1.42-1.87)	1.78 (1.35-2.33)	1.39 (1.12-1.74)	2.00 (1.25-3.20)
Age, diabetes, SBP, smoking, TC/HDL ratio	1.64 (1.43-1.88)	1.57 (1.19-2.07)	1.39 (1.11-1.73)	1.76 (1.09-2.82)

Table A2. Hazard ratios (95% CI) for first CVD event in South Asian groups compared to ethnic European groups in New Zealand and Norway – adjusting for each risk factor in separate models with only age as covariate.

	Men		Women	
	Indian vs. European NZ	South Asians vs. Norwegians	Indian NZ vs. European NZ	South Asians vs. Norwegians
N events/N	1791/73308	436/7387	863/56126	264/8558
Adjusted for				
Age only	1.75 (1.53-2.00)	1.92 (1.48-2.49)	1.42 (1.16-1.75)	1.87 (1.21-2.87)
Age and diabetes only	1.48 (1.29-1.70)	1.64 (1.25-2.15)	1.15 (0.93-1.43)	1.52 (0.96-2.39)
Age and TC/HDL ratio only	1.77 (1.55-2.02)	1.66 (1.27-2.16)	1.41 (1.14-1.73)	1.52 (0.98-2.36)
Age and SBP only	1.84 (1.61-2.10)	2.04 (1.57-2.65)	1.47 (1.20-1.82)	1.84 (1.20-2.82)
Age and smoking only	1.84 (1.61-2.10)	2.46 (1.58-3.84)	1.67 (1.35-2.07)	1.94 (1.49-2.51)

Table A3. Age-adjusted hazard ratios for first CVD event after baseline for selected risk factors in men and women aged 30-74 years with no history of CVD, stratified by cohort, ethnicity and gender – with and without adjustment for medication at baseline.

MEN	N events/N[≠]	SBP (10 mm/Hg)	SBP (10 mm/Hg) adjusted for BP medication	TC/HDL ratio (one unit)	TC/HDL ratio (one unit) adjusted for lipid lowering medication
New Zealand cohort		HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
European men	1518/63316	1.15 (1.12-1.18)	1.14 (1.11-1.17)	1.20 (1.16-1.23)	1.20 (1.16-1.24)
Indian men	273/9997	1.05 (0.98-1.13)	1.03 (0.96-1.11)	1.08 (0.98-1.19)	1.10 (1.00-1.20)
Norwegian cohort					
Norwegian men	379/6385	1.15 (1.08-1.22)	1.13 (1.06-1.20)	1.22 (1.15-1.30)	1.23 (1.16-1.31)
South Asian men	79/1239	1.17 (1.01-1.35)	1.14 (0.98-1.32)	1.23 (1.05-1.42)	1.21 (1.04-1.42)

WOMEN	N events/N[≠]	SBP(10 mm/Hg)	SBP (10 mm/Hg) adjusted for BP medication	TC/HDL ratio (one unit)	TC/HDL ratio (one unit) adjusted for lipid lowering medication
New Zealand cohort		HR (95%CI)		HR (95%CI)	
European women	757/49094	1.09 (1.05-1.13)	1.07 (1.03-1.12)	1.14 (1.09-1.21)	1.15 (1.09-1.21)
Indian women	106/7039	1.27 (1.16-1.39)	1.23 (1.12-1.36)	1.21 (1.03-1.41)	1.22 (1.04-1.42)
Norwegian cohort					
Norwegian women	259/8015	1.20 (1.12-1.28)	1.18 (1.11-1.26)	1.30 (1.19-1.43)	1.33 (1.21-1.46)
South Asian women	26/967	1.06 (0.86-1.30)	1.06 (0.85-1.31)	1.04 (0.77-1.39)	1.01 (0.75-1.37)

[≠]The numbers of events and people included in the analyses may differ due to missing risk factor data. Few were missing in the NZ cohort. SBP, systolic blood pressure; TC, total cholesterol; HDL, high density lipoprotein.

Table A4. Hazard ratios (95% CI) for first CVD event in South Asian groups compared to ethnic European groups in New Zealand and Norway – with and without adjustment for medication at baseline.

	Men		Women	
	Indian vs. European NZ	South Asians vs. Norwegians	Indian NZ vs. European NZ	South Asians vs. Norwegians
N events/N	1791/73308	436/7387	863/56126	264/8558
Adjusted for				
Age, TC/HDL ratio, diabetes, SBP, smoking	1.64 (1.43-1.88)	1.57 (1.19-2.07)	1.39 (1.11-1.73)	1.76 (1.09-2.82)
Age, TC/HDL ratio, diabetes, SBP, smoking + medication use at baseline (antihypertensives and lipid lowering drugs)	1.62 (1.41-1.86)	1.53 (1.16-2.03)	1.37 (1.10-1.71)	1.71 (1.05-2.76)

HDL, high density lipoprotein; NZ, New Zealand; SBP, systolic blood pressure; TC, Total cholesterol. All had complete information on the risk factors

Table A5. Crude rates and age-adjusted HR of CVD by risk factors, Norwegian and South Asian men from the Norwegian cohort.

	Norwegian				South Asian			
	No. of persons	No. of CVD events	Crude rate/100 000 person-years (95% CI)	HR (95% CI)	No. of persons	No. of CVD events	Crude rate/100 000 person-years (95% CI)	HR (95% CI)
Total	6385	379	703 (636-778)		1239	79	833 (668-1039)	
Diabetes								
No	6167	339	649 (583-721)	1.00	1088	59	704 (545-908)	1.00
Yes	101	28	3936 (2718-5701)	3.15 (2.14-4.65)	103	16	2166 (1327-3536)	1.61 (0.90-2.86)
Missing	*117*	*12*	*539 (298-973)*		*48*	*4*	*1110 (416-2956)*	
SBP								
<140	4701	198	493 (429-566)	1.00	1068	56	682 (525-886)	1.00
140-159	1373	130	1150 (969-1366)	1.39 (1.10-1.74)	150	19	1681 (1072-2636)	1.44 (0.83-2.49)
>160	296	51	2228 (1693-2932)	1.76 (1.28-2.42)	21	4	2865 (1075-7634)	1.51 (0.53-4.28)
Missing	*15*	*0*			*0*	*0*		
TC/HDL ratio								
<5	4284	207	568 (495-650)	1.00	538	21	499 (325-765)	1.00
≥5	2090	170	980 (843-1139)	1.64 (1.34-2.00)	698	58	1105 (854-1430)	2.14 (1.30-3.52)
Missing	*11*	*2*	*2328 (582-9307)*		*3*	*0*		
TC								
< 5 mmol/L	1930	68	410 (324-520)	1.00	407	19	609 (389-955)	1.00
≥ 5 mmol/L	4444	309	830 (742-927)	1.17 (0.90-1.53)	830	60	945 (734-1217)	1.49 (0.89-2.49)
Missing	*11*	*2*	*2328 (582-9307)*		*2*	*0*		
HDL								
<1.00 mmol/L	1032	78	915 (733-1142)	1.00	525	34	855 (611-1197)	1.00
≥1.00 mmol/L	5343	299	660 (589-739)	0.61 (0.47-0.78)	711	45	821 (613-1099)	0.99 (0.63-1.55)
Missing	*10*	*2*	*2608 (652-10427)*		*3*	*0*		
Current daily smokers								
No	4706	231	578 (508-657)	1.00	905	52	749 (571-983)	1.00
Yes	1660	146	1062 (903-1248)	1.86 (1.51-2.29)	302	25	1088 (735-1610)	1.43 (0.88-2.30)
Missing	*19*	*2*	*1236 (309-4941)*		*32*	*2*	*831 (208-3323)*	

CI, confidence interval; CVD, cardiovascular disease; HDL, high density lipoprotein; HR, hazard ratio: TC, total cholesterol; SBP, systolic blood pressure

Table A6. Crude rates and age-adjusted HR of CVD by risk factors, Norwegian and South Asian women from the Norwegian cohort.

	Norwegian				South Asian			
	No. of persons	No. of CVD events	Crude rate/100 000 person-years (95% CI)	HR (95% CI)	No. of persons	No. of CVD events	Crude rate/100 000 person-years (95% CI)	HR (95% CI)
Total	8015	259	378 (335-427)		967	26	341 (232-501)	
Diabetes								
No	7657	237	361 (318-410)	1.00	816	17	262 (163-422)	1.00
Yes	105	11	1305 (723-2356)	2.79 (1.52-5.11)	100	9	1212 (630-2329)	2.74 (1.21-6.22)
Missing	*253*	*11*	*539 (298-973)*		*51*	*0*		
SBP								
<140	6823	151	257 (219-302)	1.00	876	18	260 (164-412)	1.00
140-159	920	76	999 (798-1251)	1.82 (1.37-2.43)	67	4	774 (291-2062)	1.45 (0.48-4.34)
>160	266	31	1450 (1020-2062)	2.11 (1.42-3.15)	23	4	2378 (892-6335)	2.42 (0.76-7.71)
Missing	*6*	*1*	*2128 (300-15106)*		*1*	*0*		
TC/HDL ratio								
<5	7225	203	328 (286-376)	1.00	749	17	287 (178-462)	1.00
≥ 5	781	54	833 (638-1088)	1.79 (1.33-2.42)	215	9	537 (279-1032)	1.46 (0.65-3.30)
Missing	*9*	*2*	*3122 (781-12483)*		*0*	*0*		
TC								
< 5 mmol/L	3004	44	169 (125-227)	1.00	524	8	193 (97-386)	1.00
≥ 5 mmol/L	5002	213	503 (440-576)	1.40 (1.00-1.97)	440	18	521 (328-826)	1.54 (0.65-3.64)
Missing	*9*	*2*	*3122 (781-12483)*		*3*	*0*	*.*	
HDL								
< 1.2 mmol/L	1057	52	587 (447-770)	1.00	465	12	329 (187-578)	1.00
≥1.2 mmol/L	6949	205	344 (300-395)	0.55 (0.40-0.74)	499	14	354 (210-598)	0.77 (0.36-1.69)
Missing	*9*	*2*	*3122 (781-12483)*		*3*	*0*		
Current daily smokers								
No	5461	134	285 (241-338)	1.00	883	24	344 (231-514)	1.00
Yes	2510	119	564 (471-675)	2.22 (1.73-2.84)	13	0		
Missing	*44*	*6*	*1759 (790-3916)*		*71*	*2*	*365 (91-1461)*	

CI, confidence interval; CVD, cardiovascular disease; HDL, high density lipoprotein; HR, hazard ratio: TC, total cholesterol; SBP, systolic blood pressur

Table A7. Crude rates and age-adjusted HR of CVD by risk factors, European and Indian New Zealand men from the New Zealand cohort.

	European				Indian			
	No. of persons	No. of CVD events	Crude rate/100 000 person-years (95% CI)	HR (95% CI)	No. of persons	No. of CVD events	Crude rate/100 000 person-years (95% CI)	HR (95% CI)
Total	63 319	1 518	815 (775-857)		9 997	273	933 (828-1050)	
Type 2 diabetes								
No	57 760	1 241	728 (689-770)	1.00	7 641	158	712 (610-833)	1.00
Yes	5 559	277	1739 (1546-1957)	1.92 (1.68-2.19)	2 356	115	1622 (1351-1947)	1.72 (1.34-2.20)
Missing	*0*				*0*			
SBP								
<140	42 666	776	632 (589-678)	1.00	7 888	188	805 (698-929)	1.00
140-159	16 417	514	1030 (945-1123)	1.35 (1.20-1.51)	1 723	68	1431 (1128-1814)	1.37 (1.03-1.81)
>160	4 236	228	1675 (1471-1908)	2.03 (1.75-2.36)	386	17	1462 (909-2352)	1.22 (0.74-2.02)
Missing	*0*				*0*			
TC/HDL ratio								
<5	45 177	994	756 (711-805)	1.00	6 379	178	926 (799-1072)	1.00
≥5	18 139	524	955 (876-1040)	1.58 (1.42-1.76)	3 617	95	946 (774-1157)	1.28 (1.00-1.65)
*Missing**	*3*	*0*			*1*	*0*		
TC								
< 5 mmol/L	20 226	395	879 (797-970)	1.00	4 450	103	841 (693-1020)	1.00
≥ 5 mmol/L	36 071	684	756 (702-815)	1.01 (0.89-1.14)	5 130	137	974 (824-1152)	1.36 (1.05-1.76)
*Missing**	*7 022*	*439*	*861 (785-946)*		*417*	*33*	*1114 (792-1567)*	
HDL								
< 1.00 mmol/L	2 325	55	986 (757-1284)	1.00	561	15	1327 (800-2202)	1.00
≥1.00 mmol/L	10 920	323	891 (799-993)	0.87 (0.66-1.17)	1 231	39	1140 (833-1561)	0.62 (0.33-1.14)
*Missing**	*50 074*	*1 140*	*789 (744-836)*		*8 205*	*219*	*886 (776-1011)*	
Current daily smokers								
No	55 587	1 197	733 (692-776)	1.00	9 105	242	913 (805-1035)	1.00
Yes	7 731	321	1396 (1252-1558)	2.29 (2.02-2.59)	892	31	1123 (790-1597)	1.45 (0.99-2.11)
Missing	*1*	*0*			*0*			

CI, confidence interval; CVD, cardiovascular disease; HDL, high density lipoprotein; HR, hazard ratio: TC, total cholesterol; SBP, systolic blood pressure. *The number of missing information is different for TC/HDL ratio than for TC and HDL separately. This is because the risk factors included in the PREDICT risk assessment (age, gender, smoking, diabetes, systolic BP and total cholesterol/HDL ratio) was compulsory for assessing risk. Risk factors not compulsory for risk assessment consequently have more missing information (e.g. the HDL and TC)

Table A8. Crude rates and age-adjusted HR of CVD by risk factors, European and Indian New Zealand women from the New Zealand cohort.

	European				Indian			
	No. of persons	No. of CVD events	Crude rate/100 000 person-years (95% CI)	HR	No. of persons	No. of CVD events	Crude rate/100 000 person-years (95% CI)	HR
Total	49 094	757	528 (492-567)		7 039	106	531 (439-643)	
Type 2 diabetes								
No	44 880	635	485 (448-524)	1.00	5 010	50	358 (271-472)	1.00
Yes	4 214	122	994 (832-1187)	1.93 (1.59-2.35)	2 029	56	936 (720-1216)	2.29 (1.55-3.37)
Missing	0	0			0			
SBP								
<140	32 178	395	436 (395-481)	1.00	5 370	56	371 (285-482)	1.00
140-159	13 019	258	646 (572-730)	1.22 (1.04-1.44)	1 281	34	919 (656-1286)	2.11 (1.37-3.26)
>160	3 896	104	813 (671-985)	1.42 (1.14-1.77)	388	16	1388 (851-2266)	2.99 (1.70-5.27)
Missing	1	0			0			
TC/HDL ratio								
<5	42 800	626	507 (469-549)	1.00	5 895	89	527 (428-648)	1.00
≥5	6 289	131	658 (555-781)	1.42 (1.17-1.71)	1 143	17	559 (347-898)	1.11 (0.66-1.86)
*Missing**	5	0			1	0		
TC								
< 5 mmol/L	10 940	127	515 (433-613)	1.00	3 277	57	639 (493-828)	1.00
≥5 mmol/L	32 974	415	516 (469-569)	0.96 (0.79-1.17)	3 515	37	398 (289-550)	0.62 (0.41-0.94)
*Missing**	5 180	215	561 (491-641)		247	12	689 (391-1212)	
HDL								
< 1.2 mmol/L	1 852	26	529 (360-776)	1.00	568	9	781 (406-1501)	1.00
≥1.2 mmol/L	7 985	149	578 (492-678)	0.97 (0.64-1.47)	866	14	600 (355-1013)	0.75 (0.32-1.77)
*Missing**	39 257	582	517 (477-561)		5 605	83	504 (406-625)	
Current daily smokers								
No	43 994	595	466 (430-505)	1.00	6 973	104	526 (434-638)	1.00
Yes	5 100	162	1038 (890-1211)	2.74 (2.30-3.27)	66	2	1090 (272-4357)	2.60 (0.64-10.59)
Missing	0				0			

CI, confidence interval; CVD, cardiovascular disease; HDL, high density lipoprotein; HR, hazard ratio: TC, total cholesterol; SBP, systolic blood pressure. *The number of missing information is different for TC/HDL ratio than for TC and HDL separately. This is because the risk factors included in the PREDICT risk assessment (age, gender, smoking, diabetes, systolic BP and total cholesterol/HDL ratio) was compulsory for assessing risk. Risk factors not compulsory for risk assessment consequently have more missing information (e.g. the HDL and TC).

Table A9. Hazard ratios for first **CHD** event in South Asian groups compared to ethnic European groups in New Zealand and Norway.

	Men		Women	
	Indian NZ vs. European NZ	South Asians vs. Norwegians	Indian NZ vs. European NZ	South Asians vs. Norwegians
Adjusted for				
Age	2.10 (1.79-2.46)	2.45 (1.82-3.30)	1.60 (1.22-2.10)	3.23 (1.95-5.34)
Age, TC/HDL ratio	2.13 (1.81-2.50)	2.04 (1.51-2.76)	1.58 (1.20-2.07)	2.71 (1.61-4.54)
Age, TC/HDL ratio, diabetes	1.92 (1.63-2.26)	1.68 (1.23-2.30)	1.31 (0.99-1.74)	2.24 (1.30-3.86)
Age, TC/HDL ratio, diabetes, systolic BP	2.00 (1.70-2.36)	1.81 (1.32-2.48)	1.36 (1.02-1.80)	2.26 (1.31-3.90)
Age, TC/HDL ratio, diabetes, systolic BP, smoking	2.07 (1.76-2.44)	1.86 (1.36-2.55)	1.60 (1.20-2.13)	2.84 (1.61-5.03)

HDL, high density lipoprotein; NZ, New Zealand; SBP, systolic blood pressure; TC, Total cholesterol.

All had complete information on the risk factors

VIEW Ethnicity Protocol

Ethnicity is assigned to an individual based on a prioritisation output. The prioritisation ethnicity protocol adopted by VIEW is based on the Statistics New Zealand ethnicity prioritisation method, and is the most frequently used output method in Ministry of Health statistics. The table below shows level 2 ethnicity codes and their corresponding priority. More information on prioritised output can be found in Appendix A

Table 1

Level 2 ethnic codes

Ethnic Group code	Ethnic Group code description	Ethnic Group priority	Revised VIEW priority
10	European not further defined	21	
11	NZ European	22	
12	Other European	20	
21	NZ Maori	1	
30	Pacific Island not further defined	9	
31	Samoan	7	
32	Cook Island Maori	6	
33	Tongan	5	
34	Niuean	4	
35	Tokelauan	2	
36	Fijian	3	
37	Other Pacific Island	8	
40	Asian not further defined	14	
41	Southeast Asian	10	**12**
42	Chinese	12	**11**
43	Indian	11	**10**
44	Other Asian	13	
51	Middle Eastern	17	
52	Latin American / Hispanic	15	
53	African	16	
54	Other (retired on 1/07/2009)	19	
61	Other ethnicity	18	
94	Don't know	94	
95	Refused to answer	95	
97	Response unidentifiable	97	
99	Not stated	99	

PREDICT 2015 baseline data – Unique ethnicity codes

Ethnicity data used in VIEW comes from two sources – PREDICT and Ministry of Health. When patients are enrolled into PREDICT, their ethnicity are recorded across three ethnicity inputs fields (allowing for the self-identification of up to 3 ethnicity responses). In addition, the Ministry of Health has provided us with a 2015 update of the NHI Demographic Lookup table, containing the demographic data for 7.7 million unique eNHI. Similarly, up to three ethnicity codes are provided (allowing for the self-identification of up to three ethnicity responses). In total, each patient has up to 6 codes that represent their ethnicity.

All unique responses provided from each of the ethnicity fields in the PREDICT 2015 Baseline Data

Source	Variable name	Ethnicity Codes
PREDICT 2015	**pt_ethnic_group_1**	10 11 12 21 30 31 32 33 34 35 36 37 40 41 42 43 44 51 52 53 54 441 442 443 444 44411 44412 44413 44414 44415 NA
	pt_ethnic_group_2	10 11 12 21 30 31 32 33 34 35 36 37 40 41 42 43 44 51 52 53 54 99 441 443 44411 44412 44414 NA
	pt_ethnic_group_3	10 11 12 21 30 31 32 33 34 35 36 37 40 41 42 43 44 51 52 53 54 99 441 44411 44414 NA
Ministry of Health 2015	**nhi_ethnicg1**	10 11 12 21 30 31 32 33 34 35 36 37 40 41 42 43 44 51 52 53 54 61 94 95 97 99
	nhi_ethnicg2	10 11 12 21 30 31 32 33 34 35 36 37 40 41 42 43 44 51 52 53 54 61 94 95 97 99 NA
	nhi_ethnicg3	10 11 12 21 30 31 32 33 34 35 36 37 40 41 42 43 44 51 52 53 61 97 99 NA

NB: There are no NAs in "nhi_ethnicg1"

Procedure for Ethnicity Allocation

The procedure assigns one single ethnicity to each individual. The ethnicity response (there are 6 in total) of each individual is read by the programme using the prioritisation protocol. The programme checks each of the 6 ethnicity fields of a person, and determines which single ethnicity will be assigned. The programme checks each row of data and executes the following command in this order:

1) Is this person Maori? If yes, write "NZMaori", otherwise next question.
2) Is this person Pacific? If yes, write "Pacific", otherwise next question.
3) Is this person Indian? If yes, write "Indian", otherwise next question.
4) Is this person Chinese? If yes, write "Chinese", otherwise next question.
5) Is this person Asian? If yes, write "Asian", otherwise next question.
6) Is this person MELAA? If yes, write "MELAA", otherwise next question.
7) Is this person Other? If yes, write "Other", otherwise next question.
8) Is this person European? If yes, write "European", otherwise next question.
9) Is the ethnicity unknown, not answered, not identifiable? If yes, write "No_not_stated".

NB: MELAA = Middle Eastern, Latin American, African

VIEW REVISED Procedure for Ethnicity Allocation

1) Is this person Maori? If yes, write "NZMaori", otherwise next question.
2) Is this person Pacific? If yes, write "Pacific", otherwise next question.
3) Is this person Indian? If yes, write "Indian", otherwise next question.
4) Is this person Chinese? If yes, write "Chinese", otherwise next question.
5) Is this person Asian? If yes, write "Asian", otherwise next question.
6) Is this person European? If yes, write "European", otherwise next question.
7) Is this person MELAA? If yes, write "MELAA", otherwise next question.
8) Is this person Other? If yes, write "Other", otherwise next question.
9) Is the ethnicity unknown, not answered, not identifiable? If yes, write "No_not_stated".

Multiple Ethnicities

Any individuals with multiple ethnicity responses will be assigned the higher priority of ethnicity.

Example 1 – If a patient is recorded as Maori (21) and Samoan (31), then they are recorded as "Maori". This is because the programme asks whether this person is "Maori" first. With the answer being yes, "Maori" is recorded. The programme then moves onto the next person instead of asking whether or not they are Pacific.

Example 2 – If a person is recorded as Chinese (42), Southeast Asian (41), and NZ European (11), then they are recorded as Chinese. With Chinese being the highest priority, the person is assigned "Chinese" and the programme moves onto the next person.

NB: "Asian" contains Southeast Asian (41) which has a higher priority compared to Indian and Chinese (see Table 1). However, due to its relatively small population, the Southeast Asian group will be included in the "Asian" group, and thus not prioritised over Indian or Chinese. This is the ONLY exception to the prioritisation order!

The use of "OTHER" Ethnicity

This classification should be clearly defined. The term "Other" does in fact have its own ethnicity coding. It should not be used as a category for which miscellaneous or small populations are assigned as a matter of convenience. Previously, Middle Eastern (51), Latin American/Hispanic (52), and African (53), were frequently included in the OTHER ethnic group. Since 2009 (I think), Statistics New Zealand and the MOH have adopted a new category called MELAA which incorporates codes 51-53. A distinction between MELAA and Other is therefore created. There are two codes (and there should only be two codes), for Other Ethnicity – 54 (pre-2009) and 61 (post-2009).

Original "ag_eth" Classification

Label	Code
Maori	21
Pacific	30, 31, 32, 33, 34, 35, 36, 37
Indian	43, (36 & 43)
Asian	40, 41, 42, 44, 441, 442, 443, 444, 44411, 44412, 44414
Other	51, 52, 53, 54
European	10, 11, 12, 94, 95, 96, 99," ",""

Problems with above coding convention:

- "44415" is missing from Asian group
- MELAA codes (51-53) are recorded as "Other Ethnicity"
- "Other Ethnicity" code (61) missing
- European group contains residual codes (94, 95, 96, 99," ","")
- "Chinese" are not represented clearly

Distribution of original "ag_eth" (all unique individuals at baseline)

Frequency

Asian	European	Indian	NZMaori	Other	Pacific	<NA>
45308	276933	39205	62181	8907	59305	306

NB: There should be no NA values since **nhi_ethnicg1** contains no NAs

Proportion

Asian	European	Indian	NZMaori	Other	Pacific	<NA>
0.092	0.563	0.080	0.126	0.018	0.121	0.001

NEW "view_ag_eth" Classification

Label	Code
Maori	21
Pacific	30, 31, 32, 33, 34, 35, 36, 37
Indian	43, (36 & 43)
Chinese	42
Asian	40, 41, 44, 441, 442, 443, 444, 44411, 44412, 44414, 44415
MELAA	51, 52, 53
Other	54, 61
European	10, 11, 12
No_not_stated	94, 95, 96, 99," ",""

"Other" includes individuals who write "Klingon" or "Martian" as their response.

This list of ethnic groups can be combined as suited to the individual study, however the default coding for VIEW should be that "MELAA" and "Other" will be combined into "Other". As this is a very heterogeneous group, it may be left out of analyses that focus on ethnic-specific analyses.

"No_not_stated" is defined rather than the default "NA". The reason is that the MOH have codes precisely for these situation, ranging from "Don't know" (94), "Refused to Answer" (95), to "Not Stated" (99). If you're reporting the status of everyone in your cohort of interest, this should be stated as being missing data on ethnicity and not combined with "Other", as they represent two different types of data.

In previous merges, the European group included "Other" and "NA". The new coding allows European to be more clearly defined.

Distribution of proposed new "ag_eth2" (all unique individuals at baseline)

Frequency

Asian	Chinese	European	Indian	MELAA	No_not_stated	NZMaori
18745	26563	276433	39205	6797	654	62181

Other	Pacific	<NA>
2262	59305	0

Proportion

Asian	Chinese	European	Indian	MELAA	No_not_stated	NZMaori
0.038	0.054	0.562	0.080	0.014	0.001	0.126

Other	Pacific	<NA>
0.005	0.121	0.000

Appendix A

Prioritisation Output for Ethnicity

In prioritised output, each respondent is allocated to a single ethnic group using the priority system (Mäori, Pacific peoples, Asian, other groups except NZ European; and NZ European). The aim of prioritisation is to ensure that where some need exists to assign people to a single ethnic group, ethnic groups of policy importance, or of small size, are not swamped by the NZ European ethnic group.

This output type is the one most frequently used in Ministry of Health statistics and is also widely used in the health and disability sector for funding calculations, monitoring changes in the ethnic composition of service utilisation, and so on. Its advantage is that it produces data that are easy to work with as each individual appears only once so the sum of the ethnic group populations will add up to the total New Zealand population.

When ethnicity data is to be output to the Ministry of Health National Systems and more than three ethnicities are available to send, the prioritisation method described in the protocols must be used. This will ensure consistency within the national collections.

Limitations are that prioritised output:

- places people in specific (high priority because of policy importance) ethnic groups which simplifies yet biases the resulting statistics
- over-represents some groups at the expense of others – for example, Mäori gain at the expense of Pacific peoples (approximately 31,542) and Pacific peoples gain at the expense of other groups (34,602) of which most are Pacific/European (30,018)
- goes against the principle of self-identification.

One of the main criteria stipulated in the definition of ethnicity is that a person can belong to more than one ethnic group. The ethnicity question caters for multiple responses. However, the question does not ask people to indicate the ethnic group with which they identify the most strongly; instead, prioritisation makes this choice for them. The question is to remain the same for the 2006 census so, to ensure numerator and denominator consistency (see Section 1.5), asking people to state the ethnicity with which they identify the 'most strongly' is not an option.

III

openheart

Performance of a Framingham cardiovascular risk model among Indians and Europeans in New Zealand and the role of body mass index and social deprivation

Kjersti Stormark Rabanal,[1] Haakon Eduard Meyer,[1,2] Romana Pylypchuk,[3] Suneela Mehta,[3] Randi Marie Selmer,[1] Rodney T Jackson[3]

[1]Division of Mental and Physical Health, Norwegian Institute of Public Health, Oslo, Norway
[2]Department of Community Medicine, Institute of Health and Society, University of Oslo, Oslo, Norway
[3]School of Population Health, University of Auckland, Auckland, New Zealand

Correspondence to
MSc. Kjersti Stormark Rabanal; kjersti.stormark.rabanal@fhi.no

ABSTRACT

Objectives To evaluate a Framingham 5-year cardiovascular disease (CVD) risk score in Indians and Europeans in New Zealand, and determine whether body mass index (BMI) and socioeconomic deprivation were independent predictors of CVD risk.

Methods We included Indians and Europeans, aged 30–74 years without prior CVD undergoing risk assessment in New Zealand primary care during 2002–2015 (n=256 446). Risk profiles included standard Framingham predictors (age, sex, systolic blood pressure, total cholesterol/high-density lipoprotein ratio, smoking and diabetes) and were linked with national CVD hospitalisations and mortality datasets. Discrimination was measured by the area under the receiver operating characteristics curve (AUC) and calibration examined graphically. We used Cox regression to study the impact of BMI and deprivation on the risk of CVD with and without adjustment for the Framingham score.

Results During follow-up, 8105 and 1156 CVD events occurred in Europeans and Indians, respectively. Higher AUCs of 0.76 were found in Indian men (95% CI 0.74 to 0.78) and women (95% CI 0.73 to 0.78) compared with 0.74 (95% CI 0.73 to 0.74) in European men and 0.72 (95% CI 0.71 to 0.73) in European women. Framingham was best calibrated in Indian men, and overestimated risk in Indian women and in Europeans. BMI and deprivation were positively associated with CVD, also after adjustment for the Framingham risk score, although the BMI association was attenuated.

Conclusions The Framingham risk model performed reasonably well in Indian men, but overestimated risk in Indian women and in Europeans. BMI and socioeconomic deprivation could be useful predictors in addition to a Framingham score.

INTRODUCTION

South Asians (people originating from the Indian subcontinent) constitute almost a quarter of the world's population, and have a high burden of cardiovascular disease (CVD) compared with other ethnic groups.[1] International guidelines

Key questions

What is already known about this subject?
► South Asians have a high burden of cardiovascular disease (CVD) compared with other ethnic groups.
► Although many risk prediction models exist, most prediction models are derived based on information from Caucasian populations and few studies have examined the performance of cardiovascular risk models in South Asian populations.

What does this study add?
► Our study showed that a Framingham risk model predicted the 5-year risk of CVD in Indian men reasonably well, but overestimated risk in Indian women and in European men and women.
► We also found that BMI and deprivation could be useful predictors of CVD risk in addition to a Framingham risk score.

How might this impact on clinical practice?
► Our findings demonstrate a need for improved methods for assessing cardiovascular risk in Europeans and Indians in New Zealand.

recommend calculation of absolute cardiovascular risk based on multiple risk factors.[2] [3] Cardiovascular risk prediction models facilitate identification of high-risk patients and could help reduce the excess risk of CVD in South Asians. For a risk model to be clinically useful, however, it should be externally validated, ideally in the population where it is applied.[4] Few studies have evaluated the performance of cardiovascular risk models in South Asian populations.[5]

In the Auckland and Northland regions of New Zealand, cardiovascular risk assessments have been part of routine clinical care since the establishment of the PREDICT-CVD cohort in 2002.[6] A new
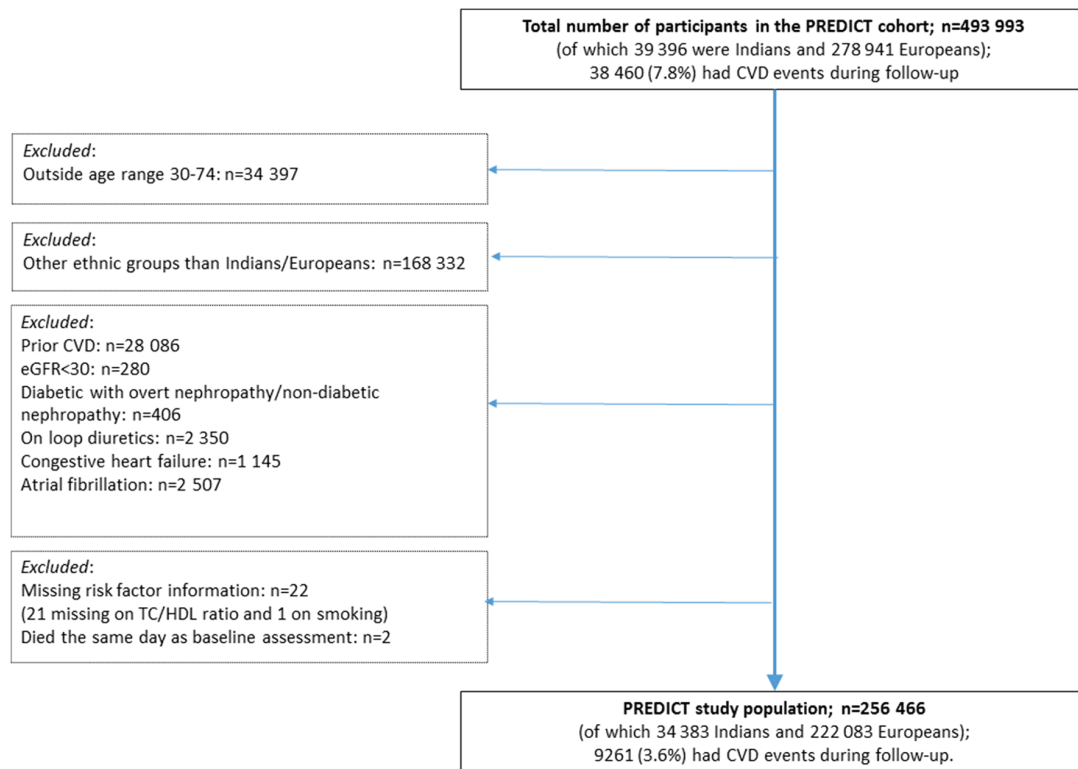
Total number of participants in the PREDICT cohort; n=493 993
(of which 39 396 were Indians and 278 941 Europeans);
38 460 (7.8%) had CVD events during follow-up

Excluded:
Outside age range 30-74: n=34 397

Excluded:
Other ethnic groups than Indians/Europeans: n=168 332

Excluded:
Prior CVD: n=28 086
eGFR<30: n=280
Diabetic with overt nephropathy/non-diabetic
nephropathy: n=406
On loop diuretics: n=2 350
Congestive heart failure: n=1 145
Atrial fibrillation: n=2 507

Excluded:
Missing risk factor information: n=22
(21 missing on TC/HDL ratio and 1 on smoking)
Died the same day as baseline assessment: n=2

PREDICT study population; n=256 466
(of which 34 383 Indians and 222 083 Europeans);
9261 (3.6%) had CVD events during follow-up.

Figure 1 Flow chart showing the numbers of persons at each stage of participant selection. CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; TC, total cholesterol.

CVD risk prediction equation for the New Zealand population has just been published,[7] but until recently, New Zealand guidelines[2] recommended general practitioners to use a modified 1991 Framingham risk equation[8] to predict patients' 5-year risk of developing CVD. This Framingham score is based on information collected >40 years ago in a cohort of white working-class and middle-class Americans.[8] The validity of Framingham for the contemporary New Zealand population has been questioned, especially regarding high-risk groups such as South Asians.[6] A previous validation study of the Framingham equation in ethnic groups in New Zealand lacked sufficient person-time follow-up to study the groups separately. Indian, Māori and Pacific people were therefore combined into one 'high-risk' group and analysed together.[9] Indians comprised only 11%–12% of this combined group.

We now have sufficient follow-up time to study the performance of the Framingham score in Indians in New Zealand. We therefore aimed to study the discrimination and calibration performance of the Framingham risk score among Indians and Europeans. Body mass index (BMI) and social deprivation are known CVD risk factors.[10 11] The second aim was to determine whether these factors improved CVD risk prediction over and above the Framingham score.

METHODS
Study population and study setting

The study population consisted of individuals risk assessed in New Zealand primary care between August 2002 and October 2015[6] using web-based decision support software called PREDICT. The PREDICT software was first implemented in Auckland general practices in 2002 and about 35%–40% of New Zealand general practices now use this software. It is mainly used in the Auckland and Northland regions, which represent around 38% of the New Zealand resident population.[12] The PREDICT study is an open cohort study continuously recruiting new participants whenever primary care practitioners complete standardised risk assessments using the PREDICT software. The study is described in detail elsewhere.[6] For these analyses, we included participants of South Asians or European ethnicity aged 30–74 years, with no history of CVD at baseline (individuals with CVD diagnosed solely in primary care, with a previous CVD hospitalisation or with congestive heart failure) (figure 1). This is a prospective cohort study, and the participants were followed until 31 December 2015.

Risk factors

Systolic blood pressure (SBP) was based on the mean of the two last recordings done by primary care practitioners. Blood lipids, glucose or glycated haemoglobin measurements were undertaken in community laboratories

while smoking status and other risk factors were gathered on a standard electronic template completed by primary care practitioners. BMI was calculated as weight in kilograms divided by the square of height in metres (kg/m^2). The exact time of the BMI measurement is unknown, but it was either at the time of the index risk assessment or before. The most recent BMI measure was used. We divided BMI into four categories: underweight (<18.5), normal weight (18.5–24.9), overweight (25.29.9) and obesity (30+). The New Zealand Index of Socioeconomic Deprivation (NZDep) is a New Zealand area-based socioeconomic deprivation score based on information from the national censuses using nine variables that reflect eight dimensions of deprivation (income, owned home, support, employment, qualifications, living space, communication and transport).[13] A deprivation score is provided for each meshblock in New Zealand. Meshblocks are geographical units defined by Statistics New Zealand. The New Zealand deprivation index relates to these small areas and not to individuals. The New Zealand deprivation index is presented as a decile score and is linked to most New Zealand health records. The deciles are based on the distribution of the first principal component score for the New Zealand deprivation index, where, decile 10 indicates residence in the 10% of the most deprived census meshblocks in New Zealand. For these analyses, we combined each set of two deciles to provide a quintile score (ie, quintile 1=deciles 1 and 2 (least deprived) through quintile 5=deciles 9 and 10 (most deprived).

Data linkage
Most New Zealanders (about 98%) have a unique National Health Identifier (NHI), assigned through contact with healthcare services in New Zealand.[14] An encrypted NHI was used to link the risk factor profiles from the PREDICT cohort with information from national health databases including all public hospitalisations, deaths, publicly funded drug dispensing and regional laboratory test results.[6]

Definition of outcome
We identified first CVD events (fatal and non-fatal) through the national hospitalisation and mortality databases using International Classification of Disease-10-Australian Modification (ICD-10-AM) codes.[15] CVD included primary and secondary hospitalisation codes or underlying cause of death from one of the following conditions: coronary heart disease (CHD), congestive heart failure, haemorrhagic or ischaemic stroke, transient ischaemic attack, peripheral vascular disease and other CVD-related deaths. Online supplementary table A1 shows the corresponding ICD-10-AM codes.

Ethnicity
Self-identified ethnicity data are routinely available for almost every New Zealander and came from the National Health Index dataset, coded according to predefined categories. In the case of multiple recorded ethnicities, a prioritising algorithm was used.[16] The ethnicity coding system for health data in New Zealand enables identification of Indian people (including Fijian Indians), but not other South Asians (such as Sri Lankans, Pakistanis, Bangladeshis or Nepalese). However, Indians account for almost 90% of South Asians in New Zealand,[17] and the majority are immigrants.[18] The Indian ethnic group does not include other Asian ethnic subgroups such as Chinese or South East Asians.

The Framingham risk score
We calculated the 5-year risk of CVD using a 1991 Framingham risk equation.[8] The Framingham predictors are age, sex, SBP, total cholesterol (TC)/high-density lipoprotein (HDL) ratio, smoking (yes/no) and diabetes (yes/no).[8] As recommended by the New Zealand Guidelines Group, individuals who recently quit smoking (within 12 months) were considered as smokers for the risk score.[2]

Statistical analyses
We measured discrimination of the Framingham score (the ability of the score to differentiate between those who experience an event and those who do not) by the area under the receiver operating characteristics (ROC) curve (AUC).[19] We additionally calculated the Harrell's C to take censoring into account.[20] We present a calibration plot of predicted minus observed event rates (calculated by the life table method) within deciles of predicted risk. When evaluating the Framingham score performance, we restricted the follow-up to maximum 5 years (counting CVD events until 5 years after baseline and resetting the person-time to 5 years for those with >5 years person-time at risk). We used Cox regression to study the impact of BMI and deprivation on the risk of CVD in Indians and Europeans with and without adjustment for the Framingham risk score. For these analyses, all available follow-up was included. Possible interaction was examined by including an interaction term in the Cox model. Only complete cases were analysed. We checked if inclusion of BMI or deprivation index in a 5-year prediction model based on Cox regression, improved AUC or Harrell's C compared with Framingham alone. Proportional hazards assumptions were tested using Schoenfeld residuals and log-log plots. All analyses were performed using Stata V.14.

Sensitivity analyses
The younger participants in PREDICT have high levels of risk factors (results not shown). We therefore repeated the calibration analyses excluding men aged <45 years and women aged <55 years to see whether calibration altered. These sex-specific age cut-offs refer to the ages when risk assessment is currently recommended for the general New Zealand population (asymptomatic and without known risk factors).[2]

Table 1 Baseline characteristics of study population, PREDICT, unadjusted

	Men		Women	
	European	**Indian**	**European**	**Indian**
N	126 736	20 210	95 347	14 173
Age in years, mean (SD)	54.4 (9.0)	46.2 (10.0)	58.8 (8.1)	52.2 (8.7)
TC/HDL ratio, mean (SD)	4.30 (1.2)	4.62 (1.2)	3.60 (1.1)	3.93 (1.0)
TC (mmol/L), mean (SD)	5.33 (1.0)	5.08 (1.0)	5.64 (1.0)	5.03 (1.0)
BMI, mean (SD)	28.5 (5.2)	26.9 (4.4)	28.1 (6.3)	28.0 (5.4)
Prevalence of obesity (BMI≥30), %	31.1	18.9	31.2	30.1
Prevalence of overweight (BMI≥25) %	78.0	66.5	65.5	70.9
SBP (mm Hg), mean (SD)	130.3 (15.9)	125.2 (15.9)	130.2 (17.2)	125.5 (17.6)
SBP≥140 mm Hg, %	29.3	19.2	30.9	22.3
Diabetes				
Type 1, %	0.7	0.4	0.6	0.4
Type 2, %	7.4	23.0	7.1	28.2
Smoking				
Never, %	68.4	83.2	73.3	98.0
Former, %	17.9	6.4	15.8	0.9
Current*, %	13.8	10.3	10.9	1.2
Family history of CVD, %	12.4	8.7	15.6	8.9
Receiving antihypertensive treatment at baseline†, %	16.7	18.2	22.4	24.2
Receiving lipid-lowering treatment at baseline†, %	14.0	22.3	14.4	22.3
New Zealand deprivation index score, five quintiles‡				
Deprivation quintile 1 (least deprived), %	31.3	10.5	30.8	12.3
Deprivation quintile 2, %	24.1	17.1	23.7	18.4
Deprivation quintile 3, %	19.3	20.5	19.8	20.3
Deprivation quintile 4, %	15.1	28.9	15.7	27.5
Deprivation quintile 5 (most deprived), %	10.2	23.1	10.0	21.5
Years of follow-up (range)	4.1 (1 day-13.3 years)	4.1 (2 days–13.2 years)	4.2 (1 day–13.3 years)	4.1 (4 days–13.1 years)

*Current smokers includes persons who recently quit (<12 months ago).
†Medication use at baseline is based on dispensing information within 6 months before baseline.
‡The quintiles are based on the distribution of the first principal component scores for the New Zealand Index of Socioeconomic Deprivation, where quintile 1 indicates residence in the 20% of the least deprived census meshblocks (geographic areas including approximately 80 people) in New Zealand.
BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; HDL, high-density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol.

RESULTS

Participant numbers and CVD events

A total of 222 083 European (43% women) and 34 383 Indian (41% women) participants aged 30–74 years without prior CVD were enrolled in the PREDICT-CVD cohort between August 2002 and December 2015. The participants were followed for a mean of 4.2 years.

During the first 5 years of follow-up, we identified 6065 CVD events among Europeans and 886 CVD events among Indians. When all available follow-up time was included, 8105 CVD events occurred among Europeans and 1156 CVD events among Indians.

Baseline characteristics

Women were older than men, and Indians around 6–8 years younger than Europeans (table 1); both age differences reflect New Zealand guideline recommendations that asymptomatic men should be risk assessed 10 years earlier than asymptomatic women and Indians 10 years earlier than Europeans.[2] TC/HDL ratios were higher in Indians than Europeans, and diabetes prevalence was more than threefold higher in Indians than Europeans. Ethnic differences in TC/HDL ratios and diabetes prevalence persisted after adjustment for age, although the differences in TC/HDL ratio diminished (not shown). Diabetes prevalence was high among the youngest

Table 2 Mean values of Framingham 5-year risk scores and observed 5-year event rates

	Men		Women	
	European	Indian	European	Indian
N	126 736	20 210	95 347	14 173
Predicted Framingham 5-year event rates (95% CI)	7.1 (7.0 to 7.1)	4.7 (4.6 to 4.7)	4.6 (4.6 to 4.6)	4.0 (3.9 to 4.0)
No. of events during 5 years of follow-up	4038	623	2 027	263
Observed 5-year event rates (life tables) (95% CI)	4.9 (4.7 to 5.0)	4.7 (4.3 to 5.1)	3.3 (3.1 to 3.4)	3.0 (2.7 to 3.4)

Performance of the Framingham risk score.

participants (not shown), also reflecting guideline recommendations that people with known risk factors or at high risk of developing diabetes should be risk assessed 10 years earlier than others.[21] People with diabetes generally have a risk assessment at the time of diagnosis and are thus automatically included in the PREDICT cohort, whatever their age.[21] Indians had lower mean SBP than Europeans, but these ethnic differences became smaller after adjustment for age (after adjusting for age the difference between the ethnic groups was 2.2 mm Hg in men and 1.5 mm Hg in women). Indians smoked less than Europeans, with minimal recorded smoking among Indian women.

Indian men had lower mean levels of BMI and were less overweight or obese than European men while Indian and European women had similar BMI levels (table 1). Indians lived in more deprived areas than Europeans with around 50% belonging to the two most deprived quintiles (quintiles 4–5). For Europeans, this percentage was around 25%.

Predicted and observed risk

Europeans had higher Framingham predicted 5-year risk than Indian participants (table 2); however, this largely reflected their older age, especially men. The observed 5-year event rates were lower than the predicted rates in all groups except Indian men where the observed and predicted event rates were similar. The observed 5-year event rates were similar in the two ethnic groups despite Europeans being considerably older than Indians.

The Framingham score discriminated better in Indians than in Europeans with AUCs of 0.76 in Indian men and women (table 3) compared with 0.74 in European men and 0.72 in European women. Harrell's C was slightly lower than the AUC for all subgroups. The Harrell's C

was also higher in Indians than in Europeans, with the highest value of 0.75 (95% CI 0.73 to 0.77) in Indian men.

The calibration plot (figure 2) showed that the Framingham 5-year risk score generally overestimated risk in higher deciles of predicted risk, especially in Europeans. The best correspondence between predicted and observed event rates was seen in Indian men.

In age-adjusted analyses, BMI was significantly associated with risk of CVD in both ethnic groups (table 4). From BMI≥18.5, we found an increasing risk of CVD with increasing BMI in both categorical and continuous analyses. After adjustment for the Framingham risk score, the continuous BMI (≥18.5) measure remained statistically significant in European men and Indian men and was borderline significant for Indian women. The HRs for this association for both Indian men and Indian women were more than double those for Europeans. However, the CIs were wide and overlapping, and there were no significant interaction between ethnicity and BMI on the risk of CVD. The categorical analyses only showed a statistically significant positive association between overweight or obesity and CVD in Indian women. Being underweight (BMI<18.5) compared with being normal weight was associated with a significantly increased risk of CVD in Europeans, which remained after adjustment for the Framingham risk score. Inclusion of BMI in the model did not increase the AUC compared with the Framingham score alone (not shown).

Quintiles of socioeconomic deprivation showed a linear association with CVD in both ethnic groups with increasing age-adjusted HRs with increasing deprivation (table 5). Compared with the least deprived quintile, the four highest deprivation quintiles (quintiles 2–5) were significantly associated with increased risk of CVD in Europeans. We found a similar pattern for Indians, although the estimates were generally lower than in Europeans and the CIs were wider. After adjusting for Framingham, all HRs were attenuated. However, the general pattern for the association between area deprivation and CVD remained in all subgroups after adjustment for Framingham. The HR for the continuous deprivation variable also remained statistically significant in all subgroups. Inclusion of deprivation index in the model did not increase the AUC compared with the Framingham alone (not shown).

Table 3 Discrimination ability of the Framingham (1991) model

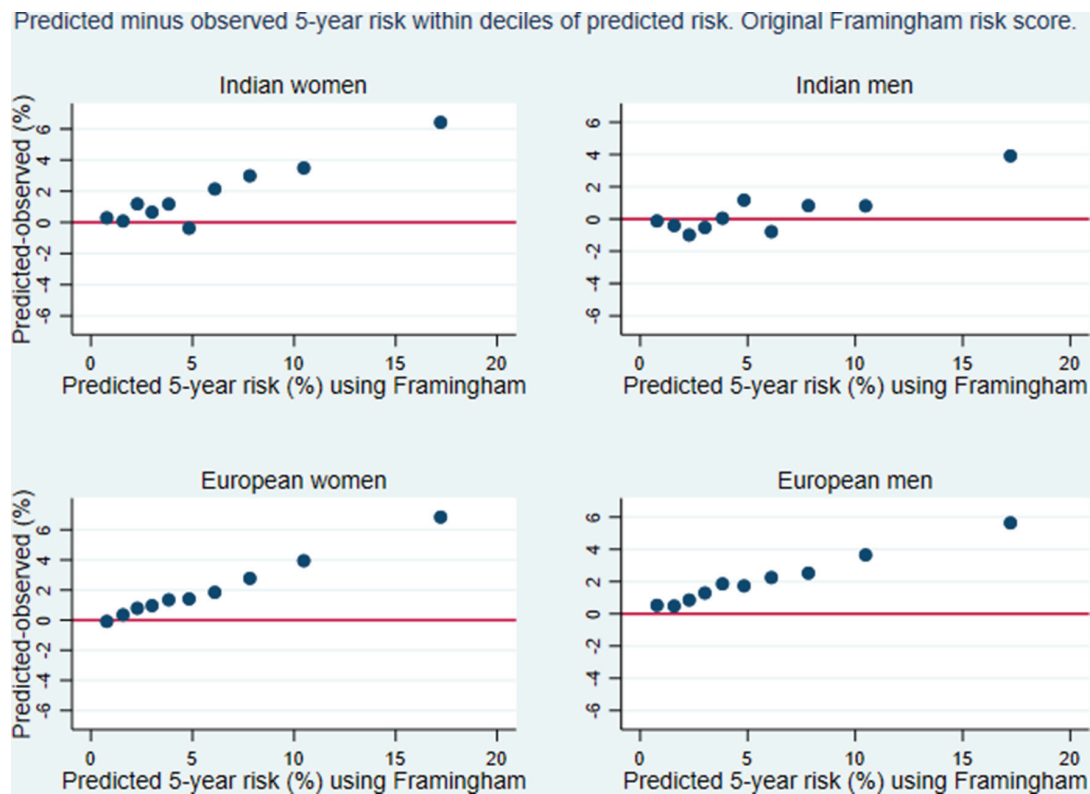|	Men		Women	
	European	Indian	European	Indian
AUC (95% CI)	0.74 (0.73 to 0.74)	0.76 (0.74 to 0.78)	0.72 (0.71 to 0.73)	0.76 (0.73 to 0.78)
Harrell's C (95% CI)	0.72 (0.71 to 0.73)	0.75 (0.73 to 0.77)	0.70 (0.69 to 0.71)	0.73 (0.70 to 0.76)

AUC, area under the curve.

Figure 2 Calibration plot showing predicted minus observed 5-year event rates within deciles of predicted risk using the original Framingham risk score by Anderson et al 1991.

Sensitivity analyses

The sensitivity analyses excluding men aged <45 years and women aged <55 years showed similar calibration (not shown).

DISCUSSION

This study showed that a Framingham CVD risk score based on risk factor information collected over 40 years ago[8] predicted the 5-year risk of CVD reasonably well in Indian men currently living in New Zealand. However, the Framingham score overestimated risk substantially in Indian women with predicted risk values of about 6% and above, and in European men and women in all but the two lowest deciles of predicted risk. Despite Indians being around 6–8 years younger than Europeans in the cohort, their observed 5-year CVD event rates were very similar to the observed 5-year CVD event rates in Europeans, consistent with the previously documented high burden of CVD in South Asians in New Zealand[22] and other countries.[1 23] We also found a positive association between increasing BMI (from BMI≥18.5) and the risk of CVD in both ethnic groups which remained statistically significant in all the subgroups except European women after adjustment for the Framingham risk score. A consistent and strong association between area deprivation and the risk of CVD in both Indians and Europeans was also identified.

It has been recommended that researchers focus on external validation of existing models instead of deriving new prediction models as there is an abundance of CVD risk scores of unclear validity.[24] This study is one of few cohort studies to evaluate the performance of an existing CVD risk score in South Asians using measures of calibration and discrimination.[5] A recent review[5] identified only four studies that reported the performance of CVD risk models in South Asians (published in English during January 2000–April 2014) and we have only been able to find one relevant study published since then.[25] A cohort study from the UK[26] was the only study identified in this review[5] to provide statistical measures of model performance (discrimination and calibration). The UK study found that Framingham underestimated risk in South Asian women and performed reasonably well in South Asian men after a factor of 1.4 was added to the score.[26] Based on these findings,[26] the previously documented high burden of CVD in South Asians[22] and New Zealand guidelines recommendations to add 5% to the risk score for South Asians,[2] we would expect the Framingham risk score to underestimate risk among Indians in New Zealand. Instead, we found that Framingham overestimated the risk in Indian women and in Europeans of both genders. This overestimation of risk could partly be explained by medical treatment since those with a high predicted risk are most likely to be prescribed medication to reduce their absolute risk of CVD.[21] Moreover, the New

Table 4 HRs (95% CI) for the prospective association between BMI and first CVD events

	N	CVD events	HR (95% CI)*	HR (95% CI)†
European men				
BMI categories				
<18.5	333	25	1.94 (1.31 to 2.89)	1.97 (1.33 to 2.94)
18.5–24.9	20 534	782	1.00 (ref)	1.00 (ref)
25–29.9	44 361	1936	1.11 (1.02 to 1.21)	0.99 (0.91 to 1.08)
30+	29 498	1622	1.45 (1.33 to 1.58)	1.06 (0.97 to 1.15)
Missing	32 010	890		
Total	126 736	5255		
BMI as continuous (per five unit increase)			1.13 (1.10 to 1.15)	1.04 (1.01 to 1.07)
BMI as continuous (per five unit increase) from BMI 18.5			1.13 (1.07 to 1.16)	1.04 (1.02 to 1.07)
Indian men				
BMI categories				
<18.5	129	6	1.13 (0.50 to 2.54)	1.37 (0.61 to 3.07)
18.5–24.9	5528	237	1.00 (ref)	1.00 (ref)
25–29.9	8044	342	1.03 (0.87 to 1.22)	0.92 (0.78 to 1.08)
30+	3193	168	1.34 (1.10 to 1.64)	1.09 (0.89 to 1.32)
Missing	3310	49		
Total	20 210	802		
BMI as continuous (per five unit increase)			1.17 (1.09 to 1.24)	1.09 (1.01 to 1.17)
BMI as continuous (per five unit increase) from BMI 18.5			1.17 (1.10 to 1.25)	1.09 (1.02 to 1.18)
European women				
BMI categories				
<18.5	889	52	2.39 (1.80 to 3.18)	2.62 (1.97 to 3.48)
18.5–24.9	22 864	574	1.00 (ref)	1.00 (ref)
25–29.9	23 524	751	1.11 (0.99 to 1.24)	0.98 (0.88 to 1.10)
30+	21 464	845	1.46 (1.31 to 1.62)	1.02 (0.92 to 1.14)
Missing	26 606	628		
Total	95 347	2850		
BMI as continuous (per five unit increase)			1.13 (1.09 to 1.16)	1.00 (0.97 to 1.03)
BMI as continuous (per five unit increase) from BMI 18.5			1.15 (1.12 to 1.18)	1.02 (0.99 to 1.06)
Indian women				
BMI categories				
<18.5	104	3	1.21 (0.38 to 3.85)	1.83 (0.57–5.83)
18.5–24.9	3319	60	1.00 (ref)	1.00 (ref)
25–29.9	4805	142	1.50 (1.11 to 2.03)	1.44 (1.07 to 1.95)
30+	3534	128	1.85 (1.36 to 2.52)	1.61 (1.18 to 2.18)
Missing	2411	21		
Total	14 173	354		
BMI as continuous (per five unit increase)			1.15 (1.06 to 1.25)	1.09 (0.99 to 1.19)
BMI as continuous (per five unit increase) from BMI 18.5			1.15 (1.06 to 1.25)	1.09 (1.00 to 1.19)

*Adjusted for age.
†Adjusted for Framingham risk score.
BMI, body mass index; CVD, cardiovascular disease.

Zealand population is a low-risk population which has experienced declining rates of CHD[27] and stroke[28] during the past four decades. It is therefore not surprising that the Framingham risk model derived from data collected over 40 years ago overpredicted the risk of CVD in European New Zealanders. The Framingham model, however,

Open Heart

Table 5 HRs (95% CI) for the prospective association between area deprivation index score and first CVD events

European men	N	CVD events	HR (95% CI)*	HR (95% CI)†
Deprivation index first quintile‡ (least deprived)	39 670	1323	1.00 (ref)	1.00 (ref)
Deprivation index second quintile	30 499	1142	1.15 (1.06 to 1.25)	1.13 (1.04 to 1.22)
Deprivation index third quintile	24 467	1066	1.31 (1.21 to 1.42)	1.23 (1.13 to 1.33)
Deprivation index fourth quintile	19 183	950	1.46 (1.34 to 1.59)	1.34 (1.23 to 1.46)
Deprivation index fifth quintile (most deprived)	12 903	774	1.68 (1.54 to 1.84)	1.48 (1.35 to 1.62)
Deprivation index missing	14	0		
Total	126 736	5255		
Deprivation index as continuous (per two unit increase on the decile score)			1.14 (1.12 to 1.16)	1.10 (1.08 to 1.13)
Indian men				
Deprivation index first quintile (least deprived)	2115	73	1.00 (ref)	1.00 (ref)
Deprivation index second quintile	3455	108	0.92 (0.69 to 1.24)	0.92 (0.68 to 1.23)
Deprivation index third quintile	4143	146	1.13 (0.86 to 1.50)	1.08 (0.82 to 1.43)
Deprivation index fourth quintile	5838	241	1.33 (1.02 to 1.72)	1.25 (0.96 to 1.63)
Deprivation index fifth quintile (most deprived)	4659	234	1.59 (1.23 to 2.07)	1.48 (1.14 to 1.93)
Deprivation index missing	0	0		
Total	20 210	802		
Deprivation index as continuous (per two unit increase on the decile score)			1.16 (1.09 to 1.22)	1.13 (1.07 to 1.20)
European women				
Deprivation index first quintile (least deprived)	29 388	639	1.00 (ref)	1.00 (ref)
Deprivation index second quintile	22 587	623	1.24 (1.11 to 1.39)	1.20 (1.08 to 1.34)
Deprivation index third quintile	18 900	557	1.28 (1.15 to 1.44)	1.22 (1.09 to 1.36)
Deprivation index fourth quintile	14 919	532	1.51 (1.34 to 1.69)	1.39 (1.24 to 1.56)
Deprivation index fifth quintile (most deprived)	9545	499	2.00 (1.78 to 2.25)	1.76 (1.57 to 1.98)
Deprivation index missing	8	0		
Total	95 347	2 850		
Deprivation index as continuous (per two unit increase on the decile score)			1.17 (1.14 to 1.20)	1.13 (1.10 to 1.16)
Indian women				
Deprivation index first quintile (least deprived)	1737	31	1.00 (ref)	1.00 (ref)
Deprivation index second quintile	2609	47	0.92 (0.59 to 1.46)	0.91 (0.58 to 1.44)
Deprivation index third quintile	2876	67	1.30 (0.85 to 1.98)	1.28 (0.83 to 1.95)
Deprivation index fourth quintile	3899	112	1.55 (1.04 to 2.31)	1.41 (0.95 to 2.10)
Deprivation index fifth quintile (most deprived)	3051	97	1.60 (1.06 to 2.39)	1.47 (0.0.98 to 2.20)
Deprivation index missing	1	0		
Total	14 173	354		
Deprivation index as continuous (per two unit increase on the decile score)			1.17 (1.07 to 1.26)	1.13 (1.04 to 1.23)

*Adjusted for age.
†Adjusted for Framingham risk score.
‡The quintiles are based on the distribution of the first principal component scores for the New Zealand Index of Socioeconomic Deprivation, where quintile 1 indicates residence in the 20% of the least deprived census meshblock areas in New Zealand.
CVD, cardiovascular disease.

was well calibrated in Indian men reflecting their previously observed increased risk.

In the present study, we found that BMI was positively associated with the risk of CVD in both Europeans and Indians in all age-adjusted analyses. After adjusting for the Framingham risk score, the categorical analyses only showed a statistically significant positive association between overweight or obesity and CVD in Indian women,

whereas when BMI was analysed as a continuous variable, the association remained significant in European men and Indian men and women. Some of the risk related to a high BMI is mediated through blood pressure, cholesterol and glucose,[11] which are included in the Framingham risk score (where diabetes is included instead of glucose). This would explain why the association between BMI and CVD was attenuated after adjusting for Framingham. BMI is often regarded as a poor indicator of adiposity in South Asians, since South Asians have higher levels of body fat than Europeans at the same BMI levels,[29] yet we found that BMI was significantly associated with the risk of CVD in Indians and Europeans. It is possible that adiposity would prove even more important for the risk of CVD in Indians had we studied other adiposity measures such as waist-to-hip ratio. Unfortunately, this information was not available for the majority of the study participants. The higher HR point estimates for the association between increasing BMI ($\geq$18.5) and CVD in Indians than Europeans could imply a stronger association between BMI and CVD in Indians, concurring with the lower cut-offs for overweight (BMI >23) and obesity (BMI >25) that has been suggested for Asian Indians.[30] However, the CIs for the two ethnic groups were overlapping. The strong association between underweight and risk of CVD is likely due to comorbidities and possibly smoking-related weight loss.[31]

We found a similar and clear association between the New Zealand deprivation index and CVD risk in both Indians and Europeans. The association persisted after adjusting for the Framingham score in both ethnic groups suggesting that information about social deprivation should be considered in addition to Framingham when assessing risk of CVD in Indians and Europeans. The ASSIGN score from Scotland[32] and QRISK,[33] which is also from the UK, are examples of risk scores that have included similar area-based measures of deprivation. Framingham risk scores have previously been criticised for lacking socioeconomic predictors[10] and our findings support the inclusion of such information. The inclusion of BMI or deprivation did not improve the AUC measures compared with Framingham alone. However, the AUC is an insensitive measure when it comes to selection of variables to be included in a prediction model.[19]

Strengths and limitations

A strength of this study is the large number of study participants and the completeness of risk factor information. Another strength is the identification of cardiovascular outcomes through comprehensive national health registers. We have also validated a well-known risk prediction model in a high-risk population in which the validity of available risk scores is largely unknown.

Since risk assessment was prioritised for high-risk patients, the PREDICT cohort may not be representative of the general New Zealand adult population. More importantly, however, the PREDICT cohort is representative of New Zealanders eligible for CVD risk assessment.

The New Zealand Ministry of Health has prioritised and incentivised heart and diabetes checks over the last 10 years through a nationally co-ordinated and funded programme.[34] Consequently, about 90% of all New Zealanders meeting national guideline eligibility criteria had CVD risk assessments between 2010 and 2015, and over 90% of eligible individuals in the primary health organisations using the PREDICT decision support software have been risk assessed. A limitation is the lack of individual measures of socioeconomic deprivation, and the lack of adiposity measures in addition to BMI, such as waist-to-hip ratio. Another limitation is that we could not distinguish between Indians born in New Zealand or overseas.

CONCLUSIONS

Prospective information from 222 000 Europeans and 34 000 Indians showed that a Framingham risk model predicted the 5-year risk of CVD in Indian men reasonably well, but overestimated risk in Indian women and in European men and women. The study also showed that BMI and deprivation are potentially useful predictors of CVD risk over and above Framingham predictors. These findings demonstrate that improved methods for assessing risk in Europeans and Indians in New Zealand are warranted, particularly given the high burden of CVD among South Asians.

REFERENCES

1. Bhopal R. Epidemic of cardiovascular disease in South Asians. Prevention must start in childhood. *Editorials BMJ* 2002;324:625–6.
2. New Zealand Guideline Group. *The assessment and Management of Cardiovascular Risk*. Wellington, New Zealand: New Zealand Guideline Group, 2003.
3. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited

experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;37:2315.

4. Altman DG, Vergouwe Y, Royston P, *et al*. Prognosis and prognostic research: validating a prognostic model. *BMJ* 2009;338:b605.
5. Gopal DP, Usher-Smith JA. Cardiovascular risk models for South Asian populations: a systematic review. *Int J Public Health* 2016;61:525–34.
6. Wells S, Riddell T, Kerr A, *et al*. Cohort Profile: The PREDICT Cardiovascular Disease Cohort in New Zealand Primary Care (PREDICT-CVD 19). *Int J Epidemiol* 2015;46.
7. Pylypchuk R, Wells S, Kerr A, *et al*. Cardiovascular disease risk prediction equations in 400 000 primary care patients in New Zealand: a derivation and validation study. *Lancet* 2018;391:1897–907.
8. Anderson KM, Odell PM, Wilson PW, *et al*. Cardiovascular disease risk profiles. *Am Heart J* 1991;121:293–8.
9. Riddell T, Wells S, Jackson R, *et al*. Performance of Framingham cardiovascular risk scores by ethnic groups in New Zealand: PREDICT CVD-10. *N Z Med J* 2010;123:50–61.
10. Fiscella K, Tancredi D, Franks P. Adding socioeconomic status to Framingham scoring to reduce disparities in coronary risk assessment. *Am Heart J* 2009;157:988–94.
11. Lu Y, Hajifathalian K, Ezzati M, *et al*. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1·8 million participants. *Lancet* 2014;383:970–83.
12. Statistics New Zealand. Subnational population estimates (RC, AU), by age and sex, at 30 June 1996, 2001, 2006-16 (2017 boundaries). 2017. http://nzdotstat.stats.govt.nz/wbos/Index.aspx?DataSetCode=TABLECODE7501
13. Department of Public Health. *Socioeconomic Deprivation Indexes: NZDep and NZiDep*. Wellington, New Zealand: University of Otago.
14. Ministry of Health. National Health Index data dictionary. 2009. http://www.health.govt.nz/publication/national-health-index-data-dictionary (Updated 01 Feb 2012).
15. Ministry of Health. *ICD-10-AM/ACHI/ACS*. Wellington, New Zealand: Ministry of Health.
16. Ministry of Health. *HISO 10001:2017 Ethnicity Data Protocols*. Wellington, New zealand: Ministry of Health, 2017.
17. Statistics New Zealand. Census ethnic group profiles: Stats NZ Tatauranga Aotearoa. 2013. http://archive.stats.govt.nz/Census/2013-census/profile-and-summary-reports/ethnic-profiles.aspx?request_value=24726#24726
18. Statistics New Zealand. Tatauranga Aotearoa. 2013 Census. Ethnic group profile: Indian. 2013. Retrived 11 Sep 2015 http://www.stats.govt.nz/Census/2013-census/profile-and-summary-reports/ethnic-profiles.aspx?request_value=24743&parent_id=24726&tabname=#
19. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. *Circulation* 2007;115:928–35.
20. Pencina MJ, D'Agostino RB, Song L. Quantifying discrimination of Framingham risk functions with different survival C statistics. *Stat Med* 2012;31:1543–53.
21. Ministry of Health. Cardiovascular Disease Risk Assessment. *New Zealand Primary Care Handbook 2012*. Wellington, New Zealand, 2013.
22. Rabanal KS, Meyer HE, Tell GS, *et al*. Can traditional risk factors explain the higher risk of cardiovascular disease in South Asians compared to Europeans in Norway and New Zealand? Two cohort studies. *BMJ Open* 2017;7:e016819.
23. Rabanal KS, Selmer RM, Igland J, *et al*. Ethnic inequalities in acute myocardial infarction and stroke rates in Norway 1994-2009: a nationwide cohort study (CVDNOR). *BMC Public Health* 2015;15:1073.
24. Damen JA, Hooft L, Schuit E, *et al*. Prediction models for cardiovascular disease risk in the general population: systematic review. *BMJ* 2016;353:i2416.
25. Joseph P, Yusuf S, Lee SF, *et al*. Prognostic validation of a non-laboratory and a laboratory based cardiovascular disease risk score in multiple regions of the world. *Heart* 2018;104:heartjnl-2017-311609.
26. Tillin T, Hughes AD, Whincup P, *et al*. Ethnicity and prediction of cardiovascular disease: performance of QRISK2 and Framingham scores in a U.K. tri-ethnic prospective cohort study (SABRE–Southall And Brent REvisited). *Heart* 2014;100:60–7.
27. Grey C, Jackson R, Wells S, *et al*. First and recurrent ischaemic heart disease events continue to decline in New Zealand, 2005-2015. *Heart* 2018;104.
28. Feigin VL, Krishnamurthi RV, Barker-Collo S, *et al*. 30-Year Trends in Stroke Rates and Outcome in Auckland, New Zealand (1981-2012): A Multi-Ethnic Population-Based Series of Studies. *PLoS One* 2015;10:e0134609.
29. Yajnik CS, Yudkin JS. The Y-Y paradox. *Lancet* 2004;363:163.
30. Misra A, Chowbey P, Makkar BM, *et al*. Consensus statement for diagnosis of obesity, abdominal obesity and the metabolic syndrome for Asian Indians and recommendations for physical activity, medical and surgical management. *J Assoc Physicians India* 2009;57:163–70.
31. Stokes A, Preston SH. Smoking and reverse causation create an obesity paradox in cardiovascular disease. *Obesity* 2015;23:2485–90.
32. Woodward M, Brindle P, Tunstall-Pedoe H. SIGN group on risk estimation. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). *Heart* 2007;93:172–6.
33. Hippisley-Cox J, Coupland C, Vinogradova Y, *et al*. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. *BMJ* 2007;335:136.
34. New Zealand Government. More Heart and Diabetes Checks Evaluation: Ministry of Health. 2016. http://www.health.govt.nz/publication/more-heart-and-diabetes-checks-evaluation

Table A1. Cardiovascular disease (CVD): included conditions and corresponding International Classification of Disease-10-Australian Modification (ICD-10-AM) codes.

CVD conditions	ICD10-AM codes
Myocardial infarction	I210-I214, I219-I221, I228, I229
Unstable angina	I200
Other coronary heart disease	I201, I208, I209, I230-I236, I238, I240, I248, I249, I253-I256, I460, I469
Heart failure	I110, I130, I132, I50, I500, I501, I509
Haemorrhagic stroke	I600-I616, I618, I619
Ischaemic stroke	I630-I636, I638, I639, I64
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,
Other CVD related deaths	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

Appendices

Appendix 1: PREDICT templates
Appendix 2: CONOR questionnaire

Appendix 1: PREDICT templates

NZ CVD / DIABETES PROGRAMME

| DEMOGRAPHICS | CVD RISK ASSESSMENT | CVD RISK MANAGEMENT | DIABETES MANAGEMENT |

[ACTIONS] [RECOMMENDATIONS] [PATIENT INFORMATION] [RISK ASSESSMENT INFO] [RESPONSE MESSAGE] [DEBUG INFO]

PAGE: DEMOGRAPHICS (DEMOGRAPHICS)

Practitioners details (1245) [PRACTITIONERS_DETAILS]

(Q_HP_ID HP_ID)
NZMC / NZNC number

Demographics (All to be prepopulated from PMS) (1246) [DEMOGRAPHICS]

(Q_PATIENT_FIRSTNAME PATIENT_FIRSTNAME)
First name

(Q_PATIENT_LASTNAME PATIENT_LASTNAME)
Last name

(Q_FIND_PLACEHOLDER_PATIENT_ID
FIND_PLACEHOLDER_PATIENT_ID)
Find Placeholder NHI?   Yes ◯ - ◯ No

(Q_NHI NHI)
NHI

(Q_DHBCATCHMENT DHBCATCHMENT)
DHB Catchment

```
Please Select (::)
Northland (:11|NLD:)
Waitemata (:21|NWA:)
Auckland (:22|CAK:)
Counties Manukau (:23|SAK:)
Waikato (:31|WKO:)
Lakes (:42|LKS:)
Bay of Plenty (:47|BOP:)
Tairawhiti (:51|TRW:)
Hawkes Bay (:61|HWB:)
Taranaki (:71|TKI:)
MidCentral (:81|MWU:)
Whanganui (:82|WNI:)
Capital and Coast (:91|CAP:)
Hutt (:92|HUT:)
Wairarapa (:93|WRP:)
Nelson Marlborough (:101|NLM:)
West Coast (:111|WCO:)
Canterbury (:121|CTY:)
South Canterbury (:123|SCY:)
Otago (:131|OTA:)
Southland (:141|SLD:)
```

(Q_NZDEP NZDEP)
Quintile of deprivation   [?]

(Q_GEOCODE GEOCODE)
Meshblock geocode   [?]

(Q_DOB DOB)
Date of birth   dd/mm/yyyy   [?]

(Q_AGE AGE)
Age   Years

(Q_GENDER GENDER)
Gender
```
Please Select (::)
Male (:M:)
Female (:F:)
```

(Q_ETHNIC_GROUP_1 ETHNIC_GROUP_1)
**Ethnic Group (1 or more self-identified ethnic group
may be chosen)**   [?]

Not Stated (::)
New Zealand European (:11:)
Other European (:12:)
New Zealand Maori (:21:)
Samoan (:31:)
Cook Island Maori (:32:)
Tongan (:33:)
Niuean (:34:)
Tokelauan (:35:)
Fijian (:36:)
Other Pacific Islands (not listed) (:37:)
Pacific Island not further defined (:30:)
Indian (:43:)
Sri Lankan (:441:)
Pakistani (:44414:)
Bangladeshi (:44412:)
Afghani (:44411:)
Nepalese (:44413:)
Tibetan (:44415:)
Chinese (:42:)
Japanese (:442:)
Korean (:443:)
Southeast Asian (:41:)
Other Asian (Code 44) (:44:)
Other Asian (Code 444) (:444:)
Asian not further defined (:40:)
Middle Eastern (:51:)
Latin American / Hispanic (:52:)
African (:53:)
Other (:54:)
European Not Further Defined (:10:)

Not Stated (:99:)
New Zealand European (:11:)
Other European (:12:)
New Zealand Maori (:21:)
Samoan (:31:)
Cook Island Maori (:32:)
Tongan (:33:)
Niuean (:34:)
Tokelauan (:35:)
Fijian (:36:)
Other Pacific Islands (not listed) (:37:)
Pacific Island not further defined (:30:)
Indian (:43:)
Sri Lankan (:441:)
Pakistani (:44414:)
Bangladeshi (:44412:)
Afghani (:44411:)
Nepalese (:44413:)
Tibetan (:44415:)
Chinese (:42:)
Japanese (:442:)
Korean (:443:)
Southeast Asian (:41:)
Other Asian (Code 44) (:44:)
Other Asian (Code 444) (:444:)
Asian not further defined (:40:)
Middle Eastern (:51:)
Latin American / Hispanic (:52:)
African (:53:)
Other (:54:)
European Not Further Defined (:10:)

(Q_ETHNIC_GROUP_2 ETHNIC_GROUP_2)
Ethnic Group 2

Not Stated (:99:)
New Zealand European (:11:)
Other European (:12:)
New Zealand Maori (:21:)
Samoan (:31:)
Cook Island Maori (:32:)
Tongan (:33:)
Niuean (:34:)
Tokelauan (:35:)
Fijian (:36:)
Other Pacific Islands (not listed) (:37:)
Pacific Island not further defined (:30:)
Indian (:43:)
Sri Lankan (:441:)
Pakistani (:44414:)
Bangladeshi (:44412:)
Afghani (:44411:)
Nepalese (:44413:)
Tibetan (:44415:)
Chinese (:42:)
Japanese (:442:)
Korean (:443:)
Southeast Asian (:41:)
Other Asian (Code 44) (:44:)
Other Asian (Code 444) (:444:)
Asian not further defined (:40:)
Middle Eastern (:51:)
Latin American / Hispanic (:52:)
African (:53:)
Other (:54:)
European Not Further Defined (:10:)

(Q_ETHNIC_GROUP_3 ETHNIC_GROUP_3)
Ethnic Group 3

NEXT ...

PAGE: CVD RISK ASSESSMENT (CVD_RISK_ASSESSMENT)

This page should be completed for all patients. All underlined items are required.

After submitting this form, additional follow up management forms become available to you. The secondary Diabetes management form will become available dependant upon the status of the Diabetes field on this form.

NOTE: It is inappropriate to do CVD risk assessment in pregnancy.

[ASSUME NEGATIVE DEFAULTS] [?]

Clinical History (1248) [CLINICAL_HISTORY]

(Q_FAMILYHISTORY FAMILYHISTORY)
Family History of Premature CVD   Yes ○ - ○ No   [?]

(Q_IHD IHD)
Angina/MI   Yes ○ - ○ No   [?]

(Q_ANGINA ANGINA)
Angina   Yes ○ - ○ No   [?]

(Q_MI MI)
MI   Yes ○ - ○ No   [?]

(Q_PTCA_CABG PTCA_CABG)
PCI/CABG   Yes ○ - ○ No   [?]

(Q_STROKE_TIA STROKE_TIA)
Ischaemic Stroke or Transient Ischaemic Attack (TIA)   Yes ○ - ○ No   [?]

(Q_STROKE STROKE)
Ischaemic Stroke   Yes ○ - ○ No   [?]

(Q_TIA TIA)
Transient Ischaemic Attack (TIA)   Yes ○ - ○ No   [?]

(Q_PVD PVD)
PVD   Yes ○ - ○ No   [?]

(Q_DIABETES DIABETES)
Diabetes   [?]

| Please select (::) |
| None (:0:) |
| Type 1 (:1:) |
| Type 2 (incl Type 2 on insulin) (:2:) |
| Type unknown (:3:) |
| Current gestational diabetes (:4:) |

(Q_ATRIAL_FIBRILLATION ATRIAL_FIBRILLATION)
ECG confirmed Atrial Fibrillation   Yes ○ - ○ No   [?]

(Q_GEN_LIPID GEN_LIPID)
Diagnosed Genetic Lipid Disorder   [?]

| Please select (::) |
| None (:0:) |
| Familial hypercholesterolaemia (:1:) |
| Familial defective apoB (:2:) |
| Familial combined dyslipidaemia (:3:) |
| Other genetic lipid disorder (:4:) |

(Q_METABOLIC_SYNDROME METABOLIC_SYNDROME)
Diagnosed metabolic syndrome   Yes ○ - ○ No   [?]

(Q_SMOKING SMOKING)
Smoking History   [?]

| Please select (::) |
| No - never (:0:) |
| No - quit over 12 months ago (:1:) |
| No - recently quit (within 12 months) (:2:) |
| Yes - up to 10 / day (:3:) |
| Yes - 11 - 19 / day (:4:) |
| Yes - 20+ / day (:5:) |

(Q_PREGNANT PREGNANT)
Pregnant?   Yes ○ - ● No   [?]

Examination (1249) [RA_EXAMINATION]

(Q_BPS BPS)
Most recent BP (Sitting)   [____] / [____] mmHg ⊞   [?]

(Q_BPS2 BPS2)
Previous BP (Sitting)   [____] / [____] mmHg   [?]

(Q_TCHDL_RATIO TCHDL_RATIO)
TC/HDL ratio   [____] - Date: [_____] dd/mm/yyyy   [?]

(Q_TCL TCL)
Total Cholesterol   [_____] mmol/L - Date: [_____] dd/mm/yyyy   [?]

Diabetes Screening (2113) [DM_SCREENING]

(Q_RA_GLUCOSE RA_GLUCOSE)
Fasting glucose (for diabetes screening)   [_____] mmol/L - Date: [_____] dd/mm/yyyy   [?]

(Q_RA_HBA1C RA_HBA1C) **HbA1c (for diabetes screening)**	[____] % - Date: [_____] dd/mm/yyyy [?]

For diabetic patient (1250) [FOR_DIABETIC_PATIENT]

(Q_DIABETES_YR DIABETES_YR) **Diabetes; year of diagnosis**	[_____] [?]
(Q_RENAL RENAL) **Renal disease**	Please select (::) / No nephropathy (:0:) / Confirmed microalbuminuria (:1:) / Overt diabetic nephropathy (:2:) / Non-diabetic nephropathy (:3:) [?]
(Q_HBA1C HBA1C) **HbA1c**	[____] % - Date: [_____] dd/mm/yyyy [?]
(Q_DataReal_1 DataReal_1) **This data is the patient's real clinical information**	Yes (●) - No (○) [?]

[SUBMIT RISK ASSESSMENT] Or [PARK ONLY]	[?]
['WHAT IF' / DEMONSTRATION STYLE RISK ASSESSMENT]	[?]

PAGE: CVD RISK MANAGEMENT (CVD_RISK_MANAGEMENT)

Note the BMI calculator on this page calculates the BMI value automatically from height and weight. All underlined items are required.

Examination (1252) [CVD_EXAMINATION]

(Q_HEIGHT HEIGHT) **Height**	[____] cm
(Q_WEIGHT WEIGHT) **Weight**	[____] kg - Date: [_____] dd/mm/yyyy
(Q_BMI BMI) **BMI (Auto-calculated)**	[____] kg/m² [?]
(Q_WAIST WAIST) **Waist circumference**	[____] cm [?]

CVD medications (1253) [CVD_MEDICATIONS]

CAUTION: Please note that all medications default to "No". Please review carefully before proceeding.

[UPDATE CVD MEDICATIONS FROM MEDTECH...]

(Q_ASPIRIN ASPIRIN) **Aspirin**	No (:0:) / Contraindicated / Not tolerated (:1:) / Yes (:2:) / Don't know (:3:) [?]
(Q_CLOPIDOGREL CLOPIDOGREL) **Clopidogrel**	No (:0:) / Contraindicated / Not tolerated (:1:) / Yes (:2:) [?]
(Q_WARFARIN WARFARIN) **Warfarin**	No (:0:) / Contraindicated / Not tolerated (:1:) / Yes (:2:)
(Q_ACE_INHIBITOR ACE_INHIBITOR) **ACE Inhibitor**	No (:0:) / Contraindicated / Not tolerated (:1:) / Yes (:2:) [?]
(Q_AT2 AT2) **Angiotensin II Receptor Blocker**	No (:0:) / Contraindicated / Not tolerated (:1:) / Yes (:2:) [?]
(Q_BETA_BLOCKER BETA_BLOCKER) **Beta Blocker**	No (:0:) / Contraindicated / Not tolerated (:1:) / Yes (:2:) [?]
(Q_THIAZIDE THIAZIDE) **Thiazide**	No (:0:) / Contraindicated / Not tolerated (:1:) / Yes (:2:) [?]
(Q_CALCIUM_ANTAGONIST CALCIUM_ANTAGONIST) **Calcium Antagonist**	No (:0:) / Contraindicated / Not tolerated (:1:) / Yes (:2:) [?]
(Q_OTHER_HYP_DRUGS OTHER_HYP_DRUGS) **Other drug therapy for Hypertension**	No (:0:) / Contraindicated / Not tolerated (:1:) / Yes (:2:) [?]
(Q_STATIN STATIN) **Statin**	No (:0:) / Contraindicated / Not tolerated (:1:) / Yes (:2:) [?]
(Q_FIBRATE FIBRATE) **Fibrate**	No (:0:) / Contraindicated / Not tolerated (:1:) / Yes (:2:) [?]

| (Q_OTHER_LIPID_DRUGS OTHER_LIPID_DRUGS) **Other Lipid lowering drugs** | No (:0:)
 Contraindicated / Not tolerated (:1:)
 Yes (:2:) | [?] |

Investigation (1254) [INVESTIGATION]

(Q_GLUCOSE GLUCOSE) **Fasting glucose (for diabetes screening)**	[____] mmol/L - Date: [_____] dd/mm/yyyy	[?]
(Q_CVD_HBA1C CVD_HBA1C) **HbA1c (for diabetes screening)**	[____] % - Date: [_____] dd/mm/yyyy	[?]
(Q_LDL LDL) **LDL Cholesterol (fasting)**	[____] mmol/L - Date: [_____] dd/mm/yyyy	[?]
(Q_TRI TRI) **Triglyceride (fasting)**	[____] mmol/L - Date: [_____] dd/mm/yyyy	[?]
(Q_HDL HDL) **HDL Cholesterol**	[____] mmol/L - Date: [_____] dd/mm/yyyy	[?]

Lifestyle Management (1255) [LIFESTYLE_MANAGEMENT]

(Q_SMK_QUIT SMK_QUIT) **Smoke Quit Advice given today?**	Yes ○ - ● No	[?]
(Q_PHY_ACTIVE PHY_ACTIVE) **Physically active?**	Yes ○ - ○ No	[?]
(Q_GREEN_PRES GREEN_PRES) **Green Prescription given**	Yes ○ - ○ No	[?]
(Q_LAST_DIET_CHECK LAST_DIET_CHECK) **Date of last dietary assessment**	[_____] dd/mm/yyyy	[?]
(Q_REFERRAL_DIET_GIVEN REFERRAL_DIET_GIVEN) **Date referral for dietary advice**	[_____] dd/mm/yyyy	[?]
(Q_Diab_nurse_edu_provided Diab_nurse_edu_provided) **Nurse Education Provided**	Yes ○ - ○ No	[?]
(Q_DataReal_2 DataReal_2) **This data is the patient's real clinical information**	Yes ● - ○ No	[?]

[NEXT ...]

[RUN CVD MANAGEMENT] Or [PARK ONLY] [?]

['WHAT IF' / DEMONSTRATION CVD MANAGEMENT] [?]

PAGE: DIABETES MANAGEMENT (DIABETES_MANAGEMENT)

All underlined items are required.

Get Checked (2062) [DIABETIC_GETCHECKED_SH]

| (Q_DIABETES_GETCHECKED DIABETES_GETCHECKED)
 Is this a Get Checked annual review? | Yes ○ - ○ No | |

Diabetes glycaemic control (1257) [DIABETES_GLYCAEMIC_CONTROL]

CAUTION: Please note that all medication-related questions in this section default to "No". Please review carefully before proceeding.

[UPDATE DM MEDICATIONS FROM MEDTECH...]

(Q_DIAB_HBA1C DIAB_HBA1C) **HbA1c**	[____] % - Date: [_____] dd/mm/yyyy	[?]
(Q_DIAB_DIETONLY DIAB_DIETONLY) **Diet therapy only**	No (:0:) Yes (:1:)	
(Q_DIAB_METFORMIN DIAB_METFORMIN) **Metformin**	No (:0:) Contraindicated / Not tolerated (:1:) Yes (:3:) On maximum tolerated dose (:2:)	[?]
(Q_DIAB_SULPHONYLUREA DIAB_SULPHONYLUREA) **Sulphonylurea**	No (:0:) Contraindicated / Not tolerated (:1:) Yes (:3:) On maximum tolerated dose (:2:)	[?]
(Q_DIAB_GLITAZONE DIAB_GLITAZONE) **Glitazone**	No (:0:) Contraindicated / Not tolerated (:1:) Yes (:3:) On maximum tolerated dose (:2:)	[?]
(Q_DIAB_ACARBOSE DIAB_ACARBOSE) **Acarbose**		

	No (:0:)
	Contraindicated / Not tolerated (:1:)
	Yes (:3:)
	On maximum tolerated dose (:2:)

(Q_DIAB_INSULIN DIAB_INSULIN)
Insulin

| No (:0:) |
| Nocturnal only (:1:) |
| Once daily (:2:) |
| Twice daily (:3:) |
| Multiple injections/insulin pump (:4:) |

(Q_DIAB_HYPO_ATTACKS DIAB_HYPO_ATTACKS)
Hypoglycaemic attacks

| No (:0:) |
| Less than 1 per month (:1:) |
| Less than 1 per week (:2:) |
| More than 1 per week (:3:) |

(Q_DIAB_LAST_DIET_ASSESS DIAB_LAST_DIET_ASSESS)
Date of last dietary assessment   [ ] dd/mm/yyyy   [?]

(Q_DIAB_DIET_REFERRAL DIAB_DIET_REFERRAL)
Date referral for dietary advice   [ ] dd/mm/yyyy   [?]

(Q_DIAB_EDU_REFERRAL DIAB_EDU_REFERRAL)
Date referral for diabetic education   [ ] dd/mm/yyyy   [?]

Renal (1258) [RENAL]

(Q_DIAB_ACR DIAB_ACR)
ACR   [ ] mg/mmol - Date: [ ] dd/mm/yyyy   [?]

(Q_SERUM_CREATININE SERUM_CREATININE)
Serum creatinine   [ ] ??/l - Date: [ ] dd/mm/yyyy   [?]

(Q_DIAB_GFR DIAB_GFR)
Estimated GFR   [ ] ml/min/1.73 m2   [?]

Diabetic Feet (required for GetChecked) (1259) [DIABETIC_FEET_HEADER]

(Q_RUNDIAB_FEET RUNDIAB_FEET)
Do you want to complete the foot section?

| No (:0:) |
| Yes (:1:) | [?]

(Q_DIAB_FEET_DATE_LAST_CHECK DIAB_FEET_DATE_LAST_CHECK)
Date of last foot examination   [ ] dd/mm/yyyy   [?]

(Q_DIAB_FEET_ULCER_HISTORY DIAB_FEET_ULCER_HISTORY)
History diabetic ulcer   Yes ◯ - ◯ No

(Q_DIAB_FEET_ULCER_CURRENT DIAB_FEET_ULCER_CURRENT)
Current diabetic ulcer   Yes ◯ - ◯ No

(Q_DIAB_FEET_HIGHRISK DIAB_FEET_HIGHRISK)
Other criteria for 'high-risk' foot   Yes ◯ - ◯ No   [?]

(Q_DIAB_FEET_PREV_LOWLIMB_AMP DIAB_FEET_PREV_LOWLIMB_AMP)
Previous diabetic lower limb amputation

| Please select (::) |
| No (:0:) |
| Yes - Left (:1:) |
| Yes - Right (:2:) |
| Yes - Bilateral (:3:) |

(Q_DIAB_FEET_SENSATION DIAB_FEET_SENSATION)
Foot - Sensation

| Please select (::) |
| Not Examined (:0:) |
| Normal (:1:) |
| Abnormal (Left) (:2:) |
| Abnormal (Right) (:3:) |
| Abnormal (BOTH) (:4:) | [?]

(Q_DIAB_FEET_CIRCULATION DIAB_FEET_CIRCULATION)
Foot - Circulation

| Please select (::) |
| Not Examined (:0:) |
| Normal (:1:) |
| Abnormal (Left) (:2:) |
| Abnormal (Right) (:3:) |
| Abnormal (BOTH) (:4:) | [?]

Diabetic Eyes (required for GetChecked) (1261) [DIABETIC_EYES_HEADER]

(Q_BLIND BLIND)
Blind in both eyes?   Yes ◯ - ⦿ No

(Q_RUNDIAB_EYES RUNDIAB_EYES)
Do you want to complete the eye section?

| No (:0:) |
| Yes (:1:) | [?]

(Q_DIAB_EYE_LASTRET DIAB_EYE_LASTRET)
Date of last retinal review   [ ] dd/mm/yyyy   [?]

(Q_DIAB_EYE_RETINOPATHY DIAB_EYE_RETINOPATHY)
Retinopathy worst eye

| Please Select (::) |
| No retinopathy / no changes (:0:) |
| Non-proliferative (:1:) |
| Proliferative (:2:) |
| Macular oedema (:3:) |
| Not checked (:9:) | [?]

(Q_DIAB_VIS_ACUITY_LEFT DIAB_VIS_ACUITY_LEFT)
Corrected visual acuity (x/x)   [ ] (L) [ ] (R)   [?]

(Q_DIAB_RETINAL_REFERRAL DIAB_RETINAL_REFERRAL)
Eye referral today?

Please Select (::)
No (:0:)
No - in screening programme (:1:)
No - under care of Ophthalmologist (:2:)
Yes - to retinal screening programme (:3:)
Yes - to ophthalmologist (:4:)

(Q_DataReal_3 DataReal_3)
This data is the patient's real clinical information Yes ⦿ - ◯ No `?`

| RUN DIABETES MANAGEMENT | Or | PARK ONLY | `?` |

| 'WHAT IF' / DEMONSTRATION DIABETES MANAGEMENT | `?` |

PAGE: Actions (Actions)

PAGE: Recommendations (Recommendations)

PAGE: Patient Information (Patient_Information)

PAGE: Risk Assessment Info (Risk_Assessment_Info)

PAGE: Response Message (Response_Message)

PAGE: Debug Info (Debug_Info)

Appendix 2: CONOR questionnaire

YOUR OWN HEALTH

1. What is your current health status? *Tick one only*
Poor
Not so good
Good
Very good

2. Do you have, or have you had?

	Yes	No	Age first time
Heart attack			
Angina pectoris (heart cramp)			
Cerebral stroke/ Brain haemorrhage			
Asthma			
Diabetes			

3. Have you during the last year suffered from pain and/or stiffness in muscles and joints that have lasted for at least 3 months ?
Yes
No

4. Have you in the last two weeks felt :

	No	A little	A lot	Very much
Nervous or worried				
Anxious				
Confident and calm				
Irritable				
Happy/Optimistic				
Down/Depressed				
Lonely				

PHYSICAL ACTIVIYY

5a. How has your physical activity during leisure time been over the last year ?
Think of your weekly average for the year. Time spent going to or fromworkk counts as leisure time
Hours per week

	None	Less than 1	1-2	3 or more
Light activity (*not sweating or out of breath*)				
Hard physical activity (*sweating/out of breath*)				

5 b. Please note physical activity during the past year in your <u>spare time</u>.
If **activity varies between summer and wintertime, note a mean value.**
(Tick one only)
Reading, watching TV or any other sedentary activity?

Walking, cycling, or other activity, other for at least 4 hours a week?
(Count also walking back and forth from work)

Light sports, heavy gardening?
(At least 4 thours perweek)

Hard exercise, competitive sports? *Regularly and several times a week*

6 . How many hours a day do you normally spend in smoke-filled rooms?
Write 0 if you don`t spend time in smoke-filled rooms
Number of hours………..

7. Did any of the adults smoke at home when you grew up?
Yes
No

8. Do you now, or have you ever lived together with a daily smoker after the age of 20 years?
Yes
No

9. Do you smoke ?
                        Yes   No
Cigarettes daily
Cigars/cigarillos daily
Pipe daily

10. If you previously smoked daily, how long is it since you quit?
………number of years

11. If you smoke daily now or previously:
How many cigarettes do you,or did you usually smoke per day?
Number of cigarettes…………….

12. How old were you when you began smoking?
………..year

13. How many years in all have you smoked daily ?

…………..years

14.a How many cups of coffee do you usually drink daily ?
Write 0 if you do not drink coffee daily
Boiled coffee (coarsely ground), number……
Coffee other, number………..

14.b What type of coffee do you usually drink?
Please tick
Filter/instant coffee
Boiled coffee (coarsely ground)
Other (espresso etc)
Do not drink coffee

14c. How many cups of coffee/tea do you usually drink daily?
Write 0 if you do not drink coffee/tea daily
Number of cups with coffee………….
Number of cups with tea…………

15 a. How many times a month do you usually drink alcohol?
Do not count low-alcohol beer. Put 0 if less than once a month.
Number of times………….

15 b. Approximately how often during the past 12 months have you consumed alcohol?
(Do not count low-alcohol beer)

4-7 times a week
2-3 times a week
App. 1 time a week
2-3 times a month
Appr. 1 time a month
A few times last year
Have not drunk alcohol the last year
Have never drunk alcohol

16 a. How many glasses of beer, wine or spirits
do you usually drink during a two-weeks period?
Do not count low-alcohol beer. Put 0 if you do not drink alcohol.

Beer…..glasses   Wine…..glasses   Spirits…..glasses

For those who have consumed alcohol during the past year
16 b. When you drank alcohol, how many glasses
 did you usually drink ?
Number of glasses………….

16 c. Approximately how often during the past 12 months have you consumed alcohol
corresponding to at least 5 glasses of spirits in 24 hours?
Number of times………..

16 d. When you drink alcohol, do you usually drink: *(Tick one or more).*
Beer   Wine   Spirits (hard liquor)

17. Are you a total abstainer from alcohol ?
Yes
No

EDUCATION

18 a. What is the highest level of education you have completed?
Less than 7 year of primary school
 7-10 years primary/secondary school
Technical school, middle school, vocational school, 1-2 years senior high school
High school diploma (3-4 years)
College/university, less than 4 years
College/university, 4 or more years

18 b. How many years education have you completed all together?
(Count every year you went to school)
Number of years………….

ILLNESS IN THE FAMILY

19. Have one or more of your parents or siblings had a heart attack
 or angina pectoris?
Yes
No
Don't know

20. Tick for those relatives who have or have had:
                        Mother   Father   Brother   Sister   Child
Cerebral stroke or
brain haemorrhage
Myocardial infarction
before age 60
Asthma

Cancer

Diabetes

Age when diabetes was first diagnosed

RESIDENCY

21. In which muncipality did you live at the age of 1 year*?*

If you did not live in Norway, give country of residence instead of municipality.

………………………..

22. What type of dwelling do you live in?

Villa/detached house

Farm

Flat/apartment

Terraced/semi-detached house

Other/institution/care home

23. How large is your home?

……….m2

24. Do you have wall-to-wall carpets in the living-room?

Yes   No

25. Is there a cat in your home?

Yes   No

FAMILY AND FRIENDS

26 a. With whom do you live? *Tick one for each question and write the number*

	Yes	No	Number
Spouse/Partner			
Other persons older than 18 years			
Persons younger than 18 years			

26 b. Do you live with anyone?

Yes

No

If YES:

	Yes	No	Number
Spouse/Partner			
Other persons older than 18 years			
Persons younger than 18 years			

26 c (only at the questionary for the elderly)

Where do you live ? *Please tick*

Home

Institution

Do you live with?

	Yes	No
Spouse/Partner?		
Other persones?		

27. How many of the children attend day care/kindergarten/nursery school?

………..

28. How many good friends do you have with whom you can talk confidentially

and who can provide help if you need it?

(Do not count people you live with, but do include other relatives)

…………………….

29. Do you feel that you have enough good friends?

Yes

No

30. How often do you usually take part in organised activities, e.g.

sewing circles, sports clubs, political meetings, religious or other organizations?

Never, or just a few times a year

1-2 times a month (before year 1996), 1-3 times a month (after year 1996)

Approximately once a week

More than once a week

WORK

31. What is your current work situation?

Paid work

Full-time housework

Under education, military service

Unemployed, on leave without payment

32 a. How many hours of paid work do you have per week?

……………….number of hours

32 b. What is your current work situation – paid work?

Yes, full-time

Yes, part time

No

33. Do you receive any of the following?

Sickness benefit?

Old-age pension?

Rehabilitation benefit?

Disability pension?

Unemployment benefits?

Social welfare benefits?

Social benefit-single parent?

34. Do you work shifts or nights?

Yes

 No

35. If you have paid or unpaid work, which statement describes your work best?

Mostly sedentary work?

(e.g. office work, mounting)

Work that requires a lot of walking?

 (e.g. shop assistant, light industrial work, teaching)

Work that requires a lot of walking and lifting?

 (e.g. postman, nursing, construction)

Heavy manual labour? *(e.g. forestry, heavy farmwork, heavy construction)*

36. Do you decide yourself how your work will be done? *(Tick one only)*

Not at all

Very little

Yes, sometimes

Yes, my own decision

37 a. Do you have any of the following occupations ?

(full time or part time) *Tick one for each question*

	Yes	No
Driver		
Farmer		
Fisherman		

37 b. What occupation/title did you have at this work?
(the question refers to another question (not CONOR) about the occupation
where they worked the longest period during the past year)
Ex secretary, teacher, industrial worker, nursing, carpenter, l
eader, salesman, driver etc)
Occupation:……………………………………………

YOUR OWN ILLNESS AND INJURIES

38. Have you ever had:
Tick one for each question. State age at event.
If it has happened several times, write age at the last event.

	Yes	No	Age at last time
Hip fracture			
Wrist/forearm fracture			
Whiplash			
Injury requiring hospital admission			

39. Do you have or have you ever had?
Tick yes or no for each question

	Yes	No
Hay fever		
Chronic bronchitis/emphysema		
Osteoporosis		
Fibromyalgia/fibrositis/chronic pain syndrome		
Psychological problems for which you have sought help		

40. Do you cough almost daily for some periods of the year?
Yes   No

41. If yes,
do you bring up phlegm?
Yes   No

42. If you cough almost daily for some periods of the year, have you had this
kind of cough for as long as 3 months in each of the last two years?
Yes   No

43. How often do you suffer from sleeplessness?
Never, or just a few times a year
1-2 times a month (before year 2000), 1-3 times a month (after year 2000)
Approximately once a week
More than once a week

44. Have you in the last twelve months suffered from sleeplessness
to the extent that it has affected your ability to work ?   Yes   No

USE OF MEDICATION

45. Do you take?

	Currently	Previously	Never

Lipid lowering drugs

Medications for high blood pressure

46 a. Have you for any length of time in the past year used any of the following
medications every day or almost daily?
Indicate how many months you have used the medication. Write 0 if you did not take the medication.

Medications:
Painkillers ………months.
Sleeping pills ………months.
Tranquilizers ………months.
Antidepressants ………months.
Allergy pills ………months.
Asthma medication ………months.
Only medication bought at pharmacy .
Do not include dietary supplements

46 b. How often during the last 4 weeks
have you taken any of the following medication?
Tick one per line

	Daily	Weekly but not daily	Less than weekly	Not taken last 4 weeks
Painkillers without prescription				
Painkillers on prescription				
Sleeping pills				
Tranquilizers				
Antidepressants				
Other medication on prescription				

46.c Fill in name of medication, reason for use and time used from q 46.b

Brand name	**Reason for use**	**For how long** **up to 1 year/1 year or more**
1.		
2.		
3.		
4.		
5.		
6.		

DIETARY SUPPLEMENTS

47 a. Have you for any length of time in the past year taken any of the
following daily or almost daily?
Indicate how many months you have used them. Write 0 if you did not take any.
Iron tablets ………..months
Vitamin D supplements ………..months
Other vitamin supplements ………..months
Cod liver oil ………..months

47 b. Do you take any of the following?

	Yes, daily	Sometimes	No
Cod liver oil, capsules			
Fish oil capsules			
Vitamin and or mineral supplements			

THE REST OF THE FORM SHOULD ONLY BE FILLED IN BY WOMEN

48. How old were you when you started menstruating?
………..year

49. If you no longer menstruate, how old were you when you stopped menstruating?
………..year

50. Are you pregnant at the moment?

Yes   No   Unsure   Postmenopausal

51. How many children have you given birth to?
………children

52. If you have given birth, what year was the child born and how many months did you breastfeed each child

Child	Year born	Number of months with breastfeeding
1.		
2.		
3.		
4.		
5.		
6.		

53. Do you use or have you ever used:

	Now	Previously	Never
Contraceptive pills (OC) (incl. minipill)			
Contraceptive injections			
Hormonal intrauterine device			
Estrogen (tablets or patches)			
Estrogen (cream or suppositories)			

54. If you use contraceptive pills, hormonal intrauterine device, or estrogen, what brand do you currently use?
………………………………………………