Cardiovascular disease and ethnicity

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

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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.
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Stavanger, September 2018
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


Terms and abbreviations

**Terms**

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country of birth</td>
<td>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).</td>
</tr>
<tr>
<td>Ethnic Norwegians</td>
<td>The term “ethnic Norwegians” refers to persons born in Norway (synonym to “Norwegian-born”). The term is mainly used in paper 1.</td>
</tr>
<tr>
<td>European</td>
<td>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).</td>
</tr>
<tr>
<td>Immigrant</td>
<td>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.</td>
</tr>
<tr>
<td>Norwegian-born</td>
<td>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.</td>
</tr>
<tr>
<td>South Asian</td>
<td>Refers to persons with their ancestry in the Indian subcontinent, including countries such as India, Pakistan, Sri Lanka, Bangladesh, Nepal and Bhutan.</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>--------------</td>
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<tr>
<td>AF</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>AMI</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>ASVD</td>
<td>Arteriosclerotic vascular disease</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the receiver operating characteristics curve</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>CHD</td>
<td>Coronary Heart Disease</td>
</tr>
<tr>
<td>CONOR</td>
<td>Cohort of Norway</td>
</tr>
<tr>
<td>CV</td>
<td>Cardiovascular</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
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<td>CVDNOR</td>
<td>The Cardiovascular Disease in Norway project</td>
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<tr>
<td>DALY</td>
<td>Disability Adjusted Life Years, described in footnote page 11</td>
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<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
</tr>
<tr>
<td>GBD</td>
<td>Global Burden of Disease</td>
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<tr>
<td>HDL</td>
<td>High-density lipoprotein</td>
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<tr>
<td>HF</td>
<td>Heart Failure</td>
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<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
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<tr>
<td>PERM</td>
<td>Percentage of Excess Risk Mediated</td>
</tr>
<tr>
<td>PREDICT</td>
<td>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.</td>
</tr>
<tr>
<td>NZ</td>
<td>New Zealand</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver operating characteristics curve</td>
</tr>
<tr>
<td>RR</td>
<td>Rate ratio</td>
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<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
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<tr>
<td>TC</td>
<td>Total cholesterol</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient Ischemic Attack</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States, refers to The United States of America</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WHR</td>
<td>Waist to hip ratio</td>
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<tr>
<td>YLL</td>
<td>Years of Life Lost, described in footnote page 11</td>
</tr>
</tbody>
</table>
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>
<thead>
<tr>
<th>Author and date, (ref)</th>
<th>Sample</th>
<th>Sex-specific analyses</th>
<th>Name of study/source and time of baseline collection</th>
<th>Number of persons and CVD cases</th>
<th>Effect measure</th>
<th>CV outcome</th>
<th>Risk factors</th>
<th>Main findings in this context</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forouhi et al. 2006, (12)</td>
<td>South Asian and European men, 40-69 years at baseline</td>
<td>Yes, the study only included men</td>
<td>The population-based Southall and Brent studies (London) between 1988 and 1991. Followed to 2006.</td>
<td>South Asians, n=1420 (108 CHD deaths) Europeans, n=1787 (94 CHD deaths)</td>
<td>HRs from Cox regression</td>
<td>CHD death</td>
<td>Age, smoking, occupation, education, BMI, waist circumference, hypertension, lipids, blood glucose, insulin resistance, diabetes and metabolic syndrome</td>
<td>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.</td>
</tr>
<tr>
<td>Williams et al. 2011, (13)</td>
<td>South Asian and White British men and women, ≥35 years at baseline</td>
<td>No, combined analyses – adjusted for sex</td>
<td>Data from Health Survey for England, 1999 and 2004. Followed to 2008.</td>
<td>South Asians, n=2120 (33 CHD deaths) White British, n=13293 (195 CHD deaths)</td>
<td>HRs from Cox regression</td>
<td>CHD death</td>
<td>Age, gender, BMI, hypertension, diabetes, smoking, physical activity, education, occupation and income</td>
<td>Major risk factors (hypertension, diabetes, smoking) were similarly related with the outcome in both ethnic groups</td>
</tr>
<tr>
<td>Tillin et al. 2013, (18)</td>
<td>South Asian, European and African Caribbean men and women, 40-69 years at baseline</td>
<td>No, combined analyses – adjusted for sex</td>
<td>The SABRE (Southall and Brent Revisited) study, 1988-1991. Followed to 2011.</td>
<td>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)</td>
<td>SHR from competing risks regression</td>
<td>CHD and stroke (fatal and non-fatal)</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Study Authors and Year</td>
<td>Study Population</td>
<td>Study Design</td>
<td>Sample Size and Event Count</td>
<td>Analysis Type</td>
<td>Outcome</td>
<td>Risk Factors Adjusted for</td>
<td>Additional Information</td>
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<tr>
<td>Eriksen et al. 2015, (19)</td>
<td>South Asian and European men and women, 40-69 years at baseline</td>
<td>No, combined analyses – adjusted for sex</td>
<td>The Southall arm of the SABRE study, 1988-1990. Followed to 2011.</td>
<td>HRs from Cox regression</td>
<td>CVD, CHD</td>
<td>Smoking, alcohol intake, physical activity, fruit and vegetable intake</td>
<td>Behavioural risk factors (smoking, alcohol intake, inactivity and infrequent fruit and vegetable intake) were similarly related with the outcome in both ethnic groups.</td>
<td></td>
</tr>
<tr>
<td>Eastwood et al. 2015, (20)</td>
<td>South Asians and Europeans, 40-69 years at baseline</td>
<td>No, combined analyses – adjusted for sex</td>
<td>The SABRE (Southall and Brent Revisited) study, 1988-1991. Followed to 2011.</td>
<td>SHRs from competing risks regression</td>
<td>CVD, stroke and CHD</td>
<td>Prediabetes and diabetes</td>
<td>Diabetes seemed to be similarly related with CVD, CHD and stroke in both ethnic groups. Results for prediabetes will not be elaborated here.</td>
<td></td>
</tr>
<tr>
<td>Eastwood et al. 2015, (21)</td>
<td>South Asian and European men, 40-69 years at baseline</td>
<td>Yes, the study only included men</td>
<td>The SABRE (Southall and Brent Revisited) study, 1988-1991. Followed to 2011.</td>
<td>Odds ratios from logistic regression (Cox regression was not used due to violations of the proportional hazards assumptions)</td>
<td>Stroke</td>
<td>Different blood pressure measurement: SBP, DBP, PP and MAP</td>
<td>SBP, DBP and MAP were more strongly associated with stroke risk in South Asians than in Europeans.</td>
<td></td>
</tr>
</tbody>
</table>

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/m², and an increased risk of CVD at BMI-levels below 18.5 kg/m² and from 25 kg/m² and above. The World Health Organisation (WHO) categorises overweight as BMI ≥25 kg/m² and obesity as BMI ≥30 kg/m² (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/m² - underweight; 18.5–23 kg/m² - increasing but acceptable risk; 23–27.5 kg/m² - increased risk; and ≥27.5 kg/m² - high risk (27). In 2009, the Indian Consensus Group also studied the available evidence and defined BMI of 23-24.9 kg/m² as overweight and ≥25 kg/m² 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

<table>
<thead>
<tr>
<th>Author and date, (ref)</th>
<th>Sample</th>
<th>Study design</th>
<th>Country</th>
<th>Number of persons and CVD cases</th>
<th>CV outcome</th>
<th>Risk score</th>
<th>Main findings in this context</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guha et al. 2004, (88)</td>
<td>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.</td>
<td>Retrospective case-control study</td>
<td>India</td>
<td>252 cases and 212 age and sex matched controls</td>
<td>ACS</td>
<td>Framingham 10-year</td>
<td>Among non-diabetic patients, the mean predicted risk was higher in patients than in controls (14.2% vs 8.6%, p&lt;0.01). In diabetic patients, no significant difference in predicted risk between patients and controls were found (11.4% vs 10.4%, p&gt;0.05)</td>
</tr>
<tr>
<td>Bhopal et al. 2005, (89)</td>
<td>Men and women aged 25-74 years. South Asians screened between May 1995 and March 1997.</td>
<td>Prospective cohort study (median follow-up time for the preliminary analyses of mortality was 7.1 years for South Asians)</td>
<td>The UK</td>
<td>South Asians, n=576, 19 CHD deaths and 3 stroke deaths Europeans, n=725, 22 CHD deaths and 9 stroke deaths</td>
<td>Expected CHD and stroke deaths (based on published SMRs and preliminary analyses of mortality in the Newcastle Heart Project sample population).</td>
<td>Framingham, SCORE, FINRISK (all models predicted 10-year risk)</td>
<td>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.</td>
</tr>
<tr>
<td>Jaquet et al. 2008, (90)</td>
<td>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.</td>
<td>Longitudinal cohort study (8.5 year follow-up)</td>
<td>Guadeloupe</td>
<td>Caribbean Indians, n=148, 31 CV events</td>
<td>CV outcomes requiring hospitalization (fatal and non-fatal): stroke, angina pectoris, acute CHD, acute PVD</td>
<td>Framingham 10-year</td>
<td>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.</td>
</tr>
<tr>
<td>Guha et al. 2008, (91)</td>
<td>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.</td>
<td>Retrospective case-control study (continuation of Guha et al. 2004)</td>
<td>India</td>
<td>350 cases and 293 age- and sex-matched controls</td>
<td>ACS</td>
<td>Framingham 10-year</td>
<td>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&lt;0.01). In diabetic patients, there were no significant difference in predicted risk between patients and controls (11.4% vs 10.4%, p=NS)</td>
</tr>
</tbody>
</table>
**Conclusion:** a model that better identifies high-risk patients is needed.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Description</th>
<th>Country</th>
<th>Design</th>
<th>Outcomes</th>
<th>Risk Scores</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bellary et al. 2010 (92)</td>
<td>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.</td>
<td>The UK</td>
<td>Prospective cohort study (2-year follow-up)</td>
<td>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.</td>
<td>CVD (fatal and non-fatal)</td>
<td>Framingham 10-year and the United Kingdom Prospective Diabetes Study 10-year risk score</td>
</tr>
<tr>
<td>Tillin et al. 2014, (84)</td>
<td>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.</td>
<td>The UK</td>
<td>Prospective cohort study (10-year follow-up)</td>
<td>South Asians, n=1317 Europeans, n=1803</td>
<td>First CVD events: myocardial infarction, coronary revascularisation, angina, transient ischemic attack or stroke</td>
<td>Modified Framingham 10-year (NICE) and QRISK2 10-year risk score</td>
</tr>
<tr>
<td>Kandula et al. 2014, (85)</td>
<td>South Asians from the Mediators of Atherosclerosis in South Asians Living in America Study, 40-79 years and free of atherosclerotic CVD</td>
<td>The US</td>
<td>Cross-sectional</td>
<td>South Asians, n=893</td>
<td>Baseline levels of subclinical atherosclerosis (CAC and CIMT)</td>
<td>The 2013 American Heart Association/American College of Cardiology Pooled Cohort Equations</td>
</tr>
</tbody>
</table>

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

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\(^1\) 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](image)

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/](image)

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.

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%), Māori (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
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.
Figure 4: Inclusion flow chart for the study population in paper 1.
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

Excluded:
Outside age range 30-74 years old, n= 19 691
History of CVD or AF, n=24 537
Renal disease (incl. on loop diuretics and eGFR≤29), n=1 582
Other ethnic groups than Europeans/Indians, n=77 232

PREDICT cohort, 2002 – 2012, n=252 491

PREDICT study population, n= 129 449

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
n= 180 553

CONOR, total individuals
(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
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).

\[
\text{PERM} = \frac{\text{HR (confounder adjusted)} - \text{HR (confounder and mediator adjusted)}}{\text{HR (confounder adjusted)}} \times 100
\]

Confounnder 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 medication.
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


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](image-url)  
*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.
Misclassification of risk factors

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.

![Causal diagram](image)

**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
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.
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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: “perspectives” was changed to “perspectives”