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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

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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

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ABSTRACT

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

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

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

 1.09-2.82 in women. Corresponding figures for the New Zealand cohort were 1.64; 95% Cl 1.43-1.88 in men and 1.39; 95% Cl 1.11-1.73 in women.

Conclusion Differences in TC/HDL ratio and diabetes appear to explain some of the excess risk of CVD in South Asians compared to Europeans.

Preventing dyslipidaemia and diabetes in South Asians may help reduce their excess risk of CVD.

Strengths and limitations of this study

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

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INTRODUCTION

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

The mechanisms underlying the increased risk of CVD in South Asian populations are mostly unknown[1]. Few studies have examined the prospective relationship between CVD risk factors and subsequent CVD among South Asians[4, 7-9], and there are few cohort studies including ethnic minority groups in Europe[10]. The two large and multinational case-control studies, Interheart[11] and Interstroke, [12] indicate that different populations share the same risk factors and that the relationship between risk factors and CVD is similar in different populations around the world. The Interheart study also concluded that the earlier age of AMI in South Asians can be largely attributed to higher risk factor levels at younger ages[13]. In both Norway and New Zealand, South Asians have been found to have similar or higher mean total cholesterol (TC) to high density lipoprotein (HDL) ratio and higher prevalence of diabetes compared to the European majority populations[14-17]. However, they also have lower levels of smoking (especially in women) and mean systolic blood pressure (SBP) than the European majority

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populations. Whether the higher risk of CVD among South Asians in Norway and New Zealand is due to higher levels of certain risk factors have not previously been studied.

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

MATERIAL AND METHODS

The New Zealand PREDICT-CVD cohort

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

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The PREDICT software is used in around 35% of New Zealand primary care practices mainly in the Auckland and Northland regions, [19] which serve around 1.7 million people, representing around 37 % of the New Zealand population[20]. Any patient with their CVD risk assessed by a general practitioner (GP) or practice nurse into online PREDICT-CVD forms are included in the PREDICT cohort. New Zealand CVD risk management guidelines recommend that all men over 45 years and all women over 55 years have a regular CVD risk assessment[21]. Specified high-CVD risk groups, including those of South Asian ethnicity, are recommended to undergo a risk assessment ten years earlier than the general population. We used PREDICT data from August 2002 until September 2012. Members of the cohort were enrolled and examined continuously throughout this period via their contact with the primary health care. We included individuals aged 30 to 74 years since the dataset was comprised of people undergoing a risk assessment based on a Framingham risk score intended for people in this age group[22]. Using information from the GP, hospital discharges and medication dispensing, we excluded persons with a history of CVD (CHD (including angina), stroke, TIA, peripheral vascular disease (PVD), percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)), or atrial fibrillation at baseline (n=24 537), and people with overt renal disease, those who had eGFR \leq 29 and those with prior hospitalisations for congestive heart failure or who were on loop diuretics at baseline (n=1582). Only subjects with European or Indian background were included. The risk factor measurements in the PREDICT cohort were extracted from a standardised electronic template that primary care practitioners completed. The SBP was based on the mean of the last two recordings done by the GP or practice nurse, in most cases with a manual mercury

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sphygmomanometer. Blood lipid and glucose or HbA1c measurements were carried out in the community laboratories routinely used by general practitioners and smoking status and other risk factor data was measured using a standard questionnaire completed by a primary care

practitioner.

Cohort of Norway

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

All CONOR surveys followed the same standard procedure for collection of data from self-administered questionnaires, physical measurements and blood samples. The CONOR questionnaire provided information on self-reported diabetes, smoking, use of blood pressure and/or lipid lowering medication and family history of CVD. All participants attended a clinical examination and non-fasting venous blood samples were drawn. SBP was measured by an automatic device (DINAMAP, Criticon, Tampa, FL,USA) after 2 minutes of seated resting. Three recordings were made at 1-min intervals. For the analyses we used the average of the second and third SBP measurements. The blood samples were subsequently measured for total cholesterol (TC) and HDL cholesterol[23].

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

We included participants aged 30-74 years old at baseline (n=3 871 excluded) to ensure comparable samples between the Norwegian and New Zealand data. We excluded participants not born in Norway or South Asia (n=5 651 excluded), pregnant women (n=197), and participants with prior CVD ((coronary heart disease (CHD), cerebrovascular disease, atherosclerotic disease, transient ischemic attack (TIA) and heart failure (HF)) (n=353) or atrial fibrillation (n=31) registered in the hospital data before screening.

Outcomes

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

CVD in the Norwegian cohort included the codes: ICD9: 410-414, 428, 430-438, 440, 441 except 441.7, 442, 443.9, 444; ICD10:I20-I25, I50, I60-

I69, I70-I79, G45. The CVD variable in the New Zealand PREDICT cohort also included some additional ICD10-codes (I469, J81, G460-G468, Z951,

Z955, Z958, Z959) plus a list of procedure codes (too many to be listed here). The PREDICT CVD outcome has been described elsewhere[19].

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Ethnicity

Ethnicity in the New Zealand PREDICT data was based on two sources: 1) the PREDICT template filled in by the GP and 2) the National Health Index dataset, both according to pre-defined categories. A prioritising algorithm was used to agree on one ethnicity in case of multiple ethnicities recorded. The system for coding ethnicity in New Zealand enables identification of Indian people, who account for approximately 90% of South Asian people living in New Zealand. The remaining South Asian ethnic groups are classified as part of the "Other Asian" ethnic group in national health data and so could not be included here. Indian people can include both immigrants and individuals who have been born in New Zealand with parents (or older generations) who have immigrated. The majority of this group are immigrants since 76.5% of the people who identified themselves with the Indian ethnic group in New Zealand in 2013 were born overseas[27]. For the Norwegian cohort, we used country of birth merged into larger world regions to define ethnicity[28]. We defined South Asians as individuals who migrated to Norway from Bangladesh, Myanmar, Sri Lanka, Pakistan, India or Nepal[28]. The largest share of South Asians in this dataset (95%) came from the HUBRO or the I-HUBRO study. HUBRO and I-HUBRO combined included 1145 Sri Lankans and 780 Pakistanis,[29] indicating that about 50% of the South Asian group (n=2206) in the present study are Sri Lankans and 35% are Pakistanis. In general, we refer to the ethnic groups as South Asians (South Asians in Norway and/or Indians in New Zealand) and Europeans (ethnic Norwegians and/or New-Zealanders with ethnic European origin). Most European New Zealanders are of British and Irish ancestry, of whom about three guarters were born in New Zealand.

Statistical analysis

Baseline characteristics are reported as mean values with standard deviations for continuous variables and fractions for categorical variables. We tested the differences between the ethnic groups adjusted for age by analysis of covariance. We used Cox regression models to examine the prospective relationship between baseline risk factors (blood pressure, lipids, diabetes and smoking) and time until subsequent first CVD event. People were censored if they died from other causes. Cox regression was also used to calculate hazard ratios (HRs) for CVD in South Asians versus Europeans using ethnicity as the exposure variable and adjusting for risk factors. Proportional hazards assumptions were tested using scaled Schoenfeld residuals[30]. All analyses were stratified by sex and ethnicity. Only complete cases were included in the analyses. Stata 14 was used for analyses in the Norwegian data and Stata 11 for analysis in the New Zealand data.

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

Ethics

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

RESULTS

Baseline characteristics

The final study sample from the New Zealand cohort consisted of 129 449 individuals (43% women) of European (87%) or Indian ethnicity (13%)

with no history of CVD, atrial fibrillation or renal disease. Correspondingly for the Norwegian cohort, the final study sample consisted of 16 606

individuals (54% women) born in either Norway (87%) or South Asia (13%) with no history of CVD or atrial fibrillation.

At baseline, the Norwegian cohort was younger than the New Zealand cohort, and New Zealand women were older than New Zealand men

(Table 1). In both cohorts, South Asians were younger than Europeans.

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

Norwegian cohort		Men		Women		
	Norwegian	South Asian	Norwegian	South Asian		
N	6 385	1 239	8 015	967		
Age (years)	43.7 (11.2)	41.4 (7.8)	43.9 (10.9)	40.3 (7.9)		
Age range	30.0 - 70.1	30.0 - 67.8	30.0 - 74.9	30.0 - 65.5		
TC (mmol/L)	5.60 (1.1)	5.48 (1.0)	5.41 (1.0)	4.98 (0.9)		
HDL cholesterol (mmol/L	1.31 (0.3)	1.07 (0.2)	1.62 (0.4)	1.24 (0.3)		
TC/HDL ratio	4.55 (1.4)	5.33 (1.4)	3.52 (1.1)	4.22 (1.2)		
SBP (mmHg)	132.6 (14.4)	126.6 (13.2)	124.0 (15.7)	119.1 (15.6)		
Diastolic blood pressure (mmHg)	77.6 (10.8)	76.9 (9.8)	71.5 (10.3)	70.0 (10.1)		
Hypertension [†] (%)	30	22	19	16		
Diabetes (%)	1.6	8.7	1.4	10.9		
Former smokers (%)	28	16	26	2		
Current smokers (%)	26	25	31	1		
Family history of heart disease* (%)	33	24	37	27		
Family history of stroke [#] (%)	11	3	13	4		
Antihypertensive treatment (%)	6	8	6	9		
Lipid lowering treatment (%)	4	6	3	6		
Follow-up time (years)	8.44 (1.4)	7.65 (1.4)	8.54 (1.2)	7.88 (1.1)		
		Men		Women		
New Zealand cohort						
	European	Indian	European	Indian		
N	63 319	9 997	49 094	7 039		
Age (years)	55.0 (9.3)	47.4 (9.7)	58.7 (8.7)	52.9 (8.5)		
Age range	30.0 - 74.0	30.0 - 74.0	30.0 - 74.0	30.0 - 74.0		
TC (mmol/L)	5.36 (1.1)	5.09 (1.1)	5.68 (1.1)	5.04 (1.0)		
HDL cholesterol (mmol/L	1.29 (0.4)	1.14 (0.3)	1.59 (0.5)	1.30 (0.3)		
LDL cholesterol (mmol/L)	3.3 (1.0)	2.9 (1.0)	3.4 (1.1)	2.8 (0.9)		
TC/HDL ratio	4.35 (1.3)	4.60 (1.3)	3.68 (1.1)	3.93 (1.1)		
SBP (mmHg)	131.5 (16.3)	125.3 (16.1)	131.6 (17.4)	126.1 (17.4)		

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Diastolic blood pressure (mmHg)	80.5 (10.0)	79.1 (10.4)	78.8 (9.7)	77.4 (9.8
Hypertension [†] (%)	40	34	44	39
Type 2 diabetes ^{\$} (%)	9	24	9	29
Former smokers (%)	19	6	16	1
Current smokers (%)	12	9	10	1
Family history of CVD [§] (%)	12	8	15	10
Antihypertensive treatment (%)	24	26	30	32
Lipid lowering treatment (%)	18	27	18	27
Follow-up time (years)	2.94 (2.3)	2.93 (2.0)	2.92 (2.3)	2.83 (1.9

Data are mean values (SD) for continuous variables and prevalence (%) for categorical variables. [†]Hypertension is defined as having systolic blood pressure \geq 140 mmHg or diastolic blood pressure \geq 90 mmHg or using blood pressure medication.

HDL, high density lipoprotein; LDL, low density lipoprotein; SBP, systolic blood pressure, TC, total cholesterol. *Parents or siblings have had heart attack or angina pectoris (self-report). [#]Parents or siblings have had stroke (self-report). ^S The diabetes variable in the New Zealand data includes people with diabetes of unknown type (5%) and type 2 diabetes (95%), while in the Norwegian data we could not differentiate between different types of diabetes. [§]Family history of CVD in the New Zealand data: self-reported familial history of ischemic heart disease or ischemic stroke occurring in a father or brother <55 years of age, or a mother or sister <65 years of age

South Asians had lower levels of TC and HDL and higher mean levels of TC/HDL ratios than Europeans in both Norway and New Zealand. South

Asians also had the lowest SBP levels (Table 1). These differences persisted after adjustment for age (p<0.05 for differences between ethnic

groups – results not shown).

The diabetes baseline prevalence was higher among South Asians compared to Europeans in both cohorts (Table 1). The difference in diabetes

were the same after adjustment for age (p<0.001). Antihypertensive and lipid lowering treatments were generally more prevalent among

South Asians than Europeans, and more prevalent in the New Zealand cohort compared to the Norwegian cohort. Cigarette smoking was more

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common among Europeans than South Asians, and practically none of the South Asian women smoked. Mean follow up time was significantly longer in the Norwegian cohort than in the New Zealand cohort (Table 1).

CVD events

During follow-up, we observed 743 new CVD events among the 16 606 individuals in the Norwegian cohort (139 470 person-years) and 2 654 CVD events among 129 446 individuals in the New Zealand cohort (378 874 person-years). The overall crude rates were 533 per 100 000 person-years in the Norwegian cohort and 700 per 100 000 person-years in the New Zealand cohort. Ethnic specific rates and age-adjusted HRs, for men and women in the two cohorts are shown in the Appendices (tables A1-A4).

Prospective associations between risk factors and CVD

Increasing age was significantly associated with risk of CVD in both ethnic groups in both cohorts (Table 2). The age effect was very similar within the countries for both ethnic groups and gender, but was stronger in the Norwegian cohort compared to the New Zealand cohort. After adjustment for age, the traditional CVD risk factors were positively associated with CVD in both ethnic groups, across gender and country. Whereas all the risk factor-CVD event associations were statistically significant in Europeans, the 95% CIs were wider and the results not always statistically significant among South Asians. The relationship between SBP, TC/HDL ratio, smoking and subsequent CVD appeared to be weaker in Indian men compared to European men in the New Zealand cohort. The prospective association between the risk factors and CVD changed little after adjusting for the other risk factors in addition to age (results not shown). In the sensitivity analyses where we excluded people using

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BP- and lipid lowering medication at baseline, the estimates for the prospective associations between risk factors and CVD were similar as in

the main analyses. However, for women in the New Zealand cohort, after excluding people on lipid-lowering medication, the HR for TC/HDL

ratio changed to 1.12; 95% CI 0.91-1.39 for Indian women and to 1.20; 95% CI 1.12-1.27 for European women.

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

MEN	N events/N [*]	Age (one year)	SBP (10 mm/Hg)	DBP (10 mm/Hg)	TC/HDL ratio	Diabetes (yes/no)	Current smoking
New Zealand cohort		HR (95%CI)	HR (95%CI)	HR (95%CI)	(one unit) HR (95%Cl)	HR (95%CI)	(yes/ho) HR (95%Cl)
European men Indian men	1518/63316 273/9997	1.07 (1.06-1.07) 1.06 (1.05-1.07)	1.15 (1.12-1.18) 1.05 (0.98-1.13)	1.16 (1.10-1.22) 1.02 (0.91-1.14)	1.20 (1.16-1.23) 1.08 (0.98-1.19)	1.92 (1.68-2.19) 1.72 (1.34-2.20)	2.29 (2.02-2.59) 1.45 (0.99-2.11)
<i>Norwegian cohort</i> Norwegian men South Asian men	379/6385 79/1239	1.10 (1.09-1.11) 1.11 (1.08-1.14)	1.15 (1.08-1.22) 1.17 (1.01-1.35)	1.19 (1.08-1.30) 1.21 (0.97-1.51)	1.22 (1.15-1.30) 1.23 (1.05-1.42)	3.15 (2.14-4.65) 1.61 (0.90-2.86)	1.86 (1.51-2.29) 1.43 (0.88-2.30)
WOMEN	N events/N [*]	Age (one year)	SBP(10 mm/Hg)	DBP (10 mm/Hg)	TC/HDL ratio (one unit)	Diabetes (yes/no)	Current smoking (yes/no)
New Zealand cohort		HR (95%CI)					
European women	757/49094	1.06 (1.05-1.07)	1.09 (1.05-1.13)	1.13 (1.05-1.22)	1.14 (1.09-1.21)	1.93 (1.59-2.35)	2.74 (2.30-3.27)
Indian women	106/7039	1.06 (1.03-1.08)	1.27 (1.16-1.39)	1.25 (1.03-1.50)	1.21 (1.03-1.41)	2.29 (1.55-3.37)	2.60 (0.64-10.59)
<i>Norwegian cohort</i> Norwegian women South Asian women	259/8015 26/967	1.10 (1.09-1.12) 1.14 (1.09-1.19)	1.20 (1.12-1.28) 1.06 (0.86-1.30)	1.32 (1.18-1.47) 1.07 (0.74-1.55)	1.30 (1.19-1.43) 1.04 (0.77-1.39)	2.79 (1.52-5.11) 2.74 (1.21-6.22)	2.22 (1.73-2.84) +

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

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Ethnic difference in CVD

South Asians of both genders in Norway and New Zealand had increased risk of CVD compared to the European majority populations (Table 3), being respectively 92% and 87% higher in South Asian men and women in Norway, and 75% and 42% higher in South Asian men and women in New Zealand. After adjustment for TC/HDL ratio and diabetes, the HRs for South Asians versus Europeans were reduced and no longer significant in women. Additional adjustments for SBP and smoking increased the hazard ratios again so that South Asians in both countries had significantly increased risk of CVD compared to Europeans. In the Norwegian cohort, South Asians had 57% and 76% higher risk than Europeans in men and women respectively after adjustment for age, TC/HDL ratio, diabetes, SBP and smoking. The corresponding excess risk after full adjustment was 64% for men and 39% for women in South Asians vs Europeans in the New Zealand cohort.

Table 3. Hazard ratios (95% CI) for first CVD event in South Asian groups compared to ethnic European groups in Norway and New Zealand.

	Men		Women	
	South Asians vs. Norwegians [*]	Indian vs. European NZ [*]	South Asians vs. Norwegians [*]	Indian NZ vs. European NZ [*]
N events/N Adjusted for	436/7387	1791/73308	264/8558	8631/56126
Age	1.92 (1.48-2.49)	1.75 (1.53-2.00)	1.87 (1.21-2.87)	1.42 (1.16-1.75)
Age, TC/HDL ratio	1.66 (1.27-2.16)	1.77 (1.55-2.02)	1.52 (0.98-2.36)	1.41 (1.14-1.73)
Age, TC/HDL ratio, diabetes	1.42 (1.08-1.87)	1.49 (1.30-1.71)	1.30 (0.82-2.04)	1.15 (0.92-1.42)
Age, TC/HDL ratio, diabetes, SBP	1.53 (1.16-2.01)	1.57 (1.37-1.80)	1.31 (0.83-2.07)	1.19 (0.96-1.47)
Age, TC/HDL ratio, diabetes, SBP, smoking	1.57 (1.19-2.07)	1.64 (1.43-1.88)	1.76 (1.09-2.82)	1.39 (1.11-1.73)

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

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After excluding people using lipid lowering medication in the sensitivity analyses for table 3, the HRs were more attenuated when adding TC/HDL ratio to the age-adjusted model than before the exclusion, especially for men in the New Zealand cohort (HRs: 1.61; 95%Cl 1.36-1.91 in men and 1.38; 95% Cl 1.06-1.79 in women).

This study confirmed that the traditional risk factors SBP, TC/HDL ratio, diabetes and smoking are all positively associated with risk of CVD in South Asians as well as in Europeans. The present study also confirmed that South Asians had an increased risk of CVD compared to Europeans and that ethnic differences in the distribution of TC/HDL ratio and type 2 diabetes appear to explain some of this excess risk. The main strengths of this study are the prospective study design, and inclusion of data from two countries. Unfortunately, we lacked information about duration of stay for the immigrants and the ethnic groups that we studied are heterogeneous. Strengths of CONOR data are the standardized measurements of risk factors, the linkage with disease outcomes from comprehensive national health registers and the standardized way of defining ethnicity using country of birth. A validation study examining the Oslo Health study, showed that participants with a non-western background had a lower participation rate than others[32]. This may reflect self-selection which can work both ways; healthy and resourceful people have the energy and motivation to participate or less healthy people who think their health could benefit from participating do so. Self-selection is unlikely to influence associations between risk factors and subsequent disease, but could influence the ethnic comparisons if the mechanisms were systematically different for the ethnic groups. The South Asian group in the

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Norwegian cohort was relatively small, which reduced the precision of the estimates and limited the statistical power. Another limitation in the CONOR data is missing information on some of the risk factors (see tables A1-A2 in the appendices for numbers of missing). Strengths of the PREDICT cohort are the large sample size and the completeness of risk factors included in the risk-assessment. Furthermore, comprehensive national health registers were used to identify and exclude people with prior CVD and to determine cardiovascular outcomes. In the New Zealand cohort, some recruitment bias is likely since risk assessment was initially prioritized for high-risk patients. The representativeness of the source population is, however, improving as PREDICTs coverage increases. In this study, follow-up extended to 2012 when PREDICT included 50% of guideline-eligible patients in the practices where the PREDICT software is used[33]. We did not assume that the cohorts were representative of the general populations in the two countries, but that the ethnic groups within the two cohorts should be comparable. Results from the two cohorts showed approximately the same regarding ethnic differences, which is a strength concerning the external validity of these results. A limitation in the New Zealand data is short follow-up time restricting the statistical power. Another limitation is the lack of standardized BP measurements since recorded BP can easily be affected by a range of factors including the type of device used[34]. In both cohorts, the endpoints are based on register data, including both hospital and mortality data, which enables almost complete

ascertainment of CVD events. In New Zealand, more than 95% of patients with an acute CVD event are managed by government-funded health services[19]. However, CVD events occurring among participants who travelled outside of New Zealand, those who emigrated after the index

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CVD risk assessment or among participants treated in private hospitals would not be captured in the national hospital and mortality registers[19]. We have no information about possible emigration for the New Zealand cohort, but for the Norwegian cohort we know that few people have emigrated (about 1% of the ethnic Norwegians and <3% of the South Asians who participated in the Oslo health studies had emigrated by the end of follow-up).

Our finding that the traditional major CVD risk factors contribute to the development of CVD in South Asians as in Europeans was an expected, yet important, finding since most knowledge about CVD prevention is based on studies in populations of European descent, and some have questioned whether these risk factors apply worldwide[11, 35]. This finding is in line with the large INTERHEART and INTERSTROKE case-control studies[11, 12], which reported that 90% of the population attributable risk for AMI and stroke worldwide was accounted for by respectively nine and ten (similar) risk factors, including those included in the present study. We are only aware of two other prospective studies reporting HRs for the prospective relationship between major CVD risk factors and subsequent CVD in South Asians[7, 36]. One of these studies included only men,[7] and the other showed estimates for men and women combined and did not include blood lipids[36]. These studies generally agree with our findings that traditional risk factors contribute to the development of CVD in South Asians as in Europeans[7, 36]. Also, consistent with previous reports[5, 6], we found that South Asians in both Norway and New Zealand have a higher risk of CVD compared to the European majority populations. By including all the measured risk factors (BP, TC/HDL ratio, diabetes and smoking) as adjustment variables in one

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

The excess risk of CVD among South Asians compared to Europeans in the Norwegian cohort was almost two-fold. This is comparable to what we reported previously when studying the total Norwegian population[5]. The South Asians in the New Zealand cohort had 42-75% higher risk of CVD compared to European New Zealanders which also agrees with previous New Zealand studies [6]. In both the Norwegian and New Zealand data, South Asians had higher baseline levels of dyslipidemia indicated by the TC/HDL ratio and higher diabetes prevalence compared to the European majority populations, which is in general agreement with previous knowledge from these countries [14-16]. Attenuation of the excess risk in South Asians versus Europeans was best achieved in the Cox model only including diabetes and TC/HDL ratio as covariates in addition to age. The same was found in both cohorts, clearly indicating that the unfavorable distribution of blood lipids and type 2 diabetes explains some of the higher risk of CVD in South Asians. South Asians generally have a high prevalence of metabolic risk factors related to insulin resistance, often clustered so that they match the concept of the metabolic syndrome[37-40]. A British cohort study that tested whether traditional risk factors could account for the high mortality of CHD among South Asian men compared to European men, reported that adjusting for insulin resistance, dyslipidemia and hyperglycemia in South Asians did not explain their higher risk[7]. However, they also adjusted for smoking and total cholesterol, which were both less prevalent/lower among South Asian men compared to European men.

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It is unclear why the traditional risk factors do not completely explain the excess risk of CVD in South Asians. This could be related to incomplete adjustments; due to either imprecise measurement of risk factors or that other important risk factors were not included (e.g. waist measurement, length of time since diabetes diagnosis). A number of non-conventional risk factors are also thought to partially account for the high risk of CVD in South Asians, including dysfunctional HDL, C-Reactive Protein, thrombogenic risk factors, telomere length, high homocysteine levels and low birth weight[41, 42]. Socioeconomic factors could probably also explain some of the differences in risk between the ethnic groups, but we did not have such variables. Another possibility is that risk factors work cumulatively over time in the development of atherosclerosis, and some risk factors may also work at specific and crucial time points during the life course. Measurements taken on single occasions may also lead to an underestimation of the strength between the usual levels of the risk factors and later disease, known as the regression dilution bias[43]. Consequently, it is unlikely that the ethnic differences would disappear completely by adjusting for selected risk factors measured once in midlife. Although South Asians seem to have an underlying susceptibility for metabolic diseases, traditional and modifiable risk factors are important for preventing disease. Our analyses indicate that it is important to focus on the prevention of type 2 diabetes and dyslipidaemia when aiming to reduce the burden of CVD among South Asians. The additional effect of abdominal obesity for the risk of CVD among South Asians in Norway

and New Zealand has, however, not yet been studied although we know that the prevalence is high in this ethnic group[38, 44]. In both

Norway[45, 46] and New Zealand,[47] intervention studies targeting immigrants from South Asia have been carried out with some promising

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results. A UK-study that prospectively examined the influence from four health behaviors on the risk of CVD in South Asian immigrants and UK Europeans found an important potential for disease prevention among South Asians if they adhered to healthy behaviors[8].

CONCLUSION

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

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Data sharing statement: No additional data are available.

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Appendix

Table A1. Crude rates and age-adjusted HR of CVD by risk factors, Norwegian and South Asian men from the Norwegian cohort.

	Norwegian						South Asian	
	No. of persons	No. of CVD events	Crude rate/100 000 person-years (95% CI)	HR (95% CI)	No. of persons	No. of CVD events	Crude rate/100 000 person-years (95% CI)	HR (95% CI)
Total	6385	379	703 (636-778)		1239	79	833 (668-1039)	
Diabetes								
No	6167	339	649 (583-721)	1.00	1088	59	704 (545-908)	1.00
Yes	101	28	3936 (2718-5701)	3.15 (2.14-4.65)	103	16	2166 (1327-3536)	1.61 (0.90-2.8
Missing	117	12	539 (298-973)		48	4	1110 (416-2956)	
SBP								
<140	4701	198	493 (429-566)	1.00	1068	56	682 (525-886)	1.00
140-159	1373	130	1150 (969-1366)	1.39 (1.10-1.74)	150	19	1681 (1072-2636)	1.44 (0.83-2.4
>160	296	51	2228 (1693-2932)	1.76 (1.28-2.42)	21	4	2865 (1075-7634)	1.51 (0.53-4.2
Missing	15	0			0	0		
TC/HDL ratio								
<5	4284	207	568 (495-650)	1.00	538	21	499 (325-765)	1.00
≥5	2090	170	980 (843-1139)	1.64 (1.34-2.00)	698	58	1105 (854-1430)	2.14 (1.30-3.5
Missing	11	2	2328 (582-9307)		3	0		
тс								
< 5 mmol/L	1930	68	410 (324-520)	1.00	407	19	609 (389-955)	1.00
≥ 5 mmol/L	4444	309	830 (742-927)	1.17 (0.90-1.53)	830	60	945 (734-1217)	1.49 (0.89-2.4
Missing	11	2	2328 (582-9307)		2	0		
HDL								
< 1.00 mmol/L	1032	78	915 (733-1142)	1.00	525	34	855 (611-1197)	1.00
≥1.00 mmol/L	5343	299	660 (589-739)	0.61 (0.47-0.78)	711	45	821 (613-1099)	0.99 (0.63-1.5
Missing	10	2	2608 (652-10427)		3	0		
Current daily smokers								
No	4706	231	578 (508-657)	1.00	905	52	749 (571-983)	1.00
Yes	1660	146	1062 (903-1248)	1.86 (1.51-2.29)	302	25	1088 (735-1610)	1.43 (0.88-2.3
Missing	19	2	1236 (309-4941)		32	2	831 (208-3323)	

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

APPENDIX

Table A2. Crude rates and age-adjusted HR of CVD by risk factors, Norwegian and South Asian women from the Norwegian cohort.

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

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

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APPENDIX

Table A3. Crude rates and age-adjusted HR of CVD by risk factors, European and Indian New Zealand men from the New Zealand cohort.

European						Indian			
	No. of persons	No. of CVD events	Crude rate/100 000 person-years (95% CI)	HR (95% CI)	No. of persons	No. of CVD events	Crude rate/100 000 person-years (95% CI)	HR (95% CI)	
Total	63 319	1 518	815 (775-857)		9 997	273	933 (828-1050)		
Type 2 diabetes									
No	57 760	1 241	728 (689-770)	1.00	7 641	158	712 (610-833)	1.00	
Yes	5 559	277	1739 (1546-1957)	1.92 (1.68-2.19)	2 356	115	1622 (1351-1947)	1.72 (1.34-2.2	
Missing	0				0				
SBP									
<140	42 666	776	632 (589-678)	1.00	7 888	188	805 (698-929)	1.00	
140-159	16 417	514	1030 (945-1123)	1.35 (1.20-1.51)	1 723	68	1431 (1128-1814)	1.37 (1.03-1.8	
>160	4 236	228	1675 (1471-1908)	2.03 (1.75-2.36)	386	17	1462 (909-2352)	1.22 (0.74-2.0	
Missing	0				0				
TC/HDL ratio									
<5	45 177	994	756 (711-805)	1.00	6 379	178	926 (799-1072)	1.00	
≥5	18 139	524	955 (876-1040)	1.58 (1.42-1.76)	3 617	95	946 (774-1157)	1.28 (1.00-1.6	
Missing*	3	0	Υ Υ	· ·	1	0	, , ,	,	
тс									
< 5 mmol/L	20 226	395	879 (797-970)	1.00	4 450	103	841 (693-1020)	1.00	
≥ 5 mmol/L	36 071	684	756 (702-815)	1.01 (0.89-1.14)	5 130	137	974 (824-1152)	1.36 (1.05-1.7	
Missing*	7 022	439	861 (785-946)		417	33	1114 (792-1567)	·	
HDL			. ,						
< 1.00 mmol/L	2 325	55	986 (757-1284)	1.00	561	15	1327 (800-2202)	1.00	
≥1.00 mmol/L	10 920	323	891 (799-993)	0.87 (0.66-1.17)	1 231	39	1140 (833-1561)	0.62 (0.33-1.1	
Missing*	50 074	1 140	789 (744-836)		8 205	219	886 (776-1011)		
Current daily smokers			· · · ·						
No	55 587	1 197	733 (692-776)	1.00	9 105	242	913 (805-1035)	1.00	
Yes	7 731	321	1396 (1252-1558)	2.29 (2.02-2.59)	892	31	1123 (790-1597)	1.45 (0.99-2.1	
Missina	1	0	/	- (/	0			- (

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

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APPENDIX

Table A4. Crude rates and age-adjusted HR of CVD by risk factors, European and Indian New Zealand women from the New Zealand cohort.

	_			lu d'au				
6	European		indian					
7 8 9	No. of persons	No. of CVD events	Crude rate/100 000 person-years (95% CI)	HR	No. of persons	No. of CVD events	Crude rate/100 000 person- years (95% CI)	HR
10 Total	49 094	757	528 (492-567)		7 039	106	531 (439-643)	
11 Type 2 diabetes								
12 No	44 880	635	485 (448-524)	1.00	5 010	50	358 (271-472)	1.00
13 Yes	4 214	122	994 (832-1187)	1.93 (1.59-2.35)	2 029	56	936 (720-1216)	2.29 (1.55-3
14 Missing	0				0			
15 SBP								
16 <140	32 178	395	436 (395-481)	1.00	5 370	56	371 (285-482)	1.00
17 10 140-159	13 019	258	646 (572-730)	1.22 (1.04-1.44)	1 281	34	919 (656-1286)	2.11 (1.37-3
10 >160	3 896	104	813 (671-985)	1.42 (1.14-1.77)	388	16	1388 (851-2266)	2.99 (1.70-5
20 Missing	1	0			0			
20 21 TC/HDL ratio								
22 <5	42 800	626	507 (469-549)	1.00	5 895	89	527 (428-648)	1.00
 23 ≥5	6 289	131	658 (555-781)	1.42 (1.17-1.71)	1 143	17	559 (347-898)	1.11 (0.66-1
24 Missing*	5	0			1	0		
25 тс								
26 < 5 mmol/L	10 940	127	515 (433-613)	1.00	3 277	57	639 (493-828)	1.00
27 ≥ 5 mmol/L	32 974	415	516 (469-569)	0.96 (0.79-1.17)	3 515	37	398 (289-550)	0.62 (0.41-0
28 Missing*	5 180	215	561 (491-641)		247	12	689 (391-1212)	
29 hdl								
30 < 1.2 mmol/L	1 852	26	529 (360-776)	1.00	568	9	781 (406-1501)	1.00
31 ≥1.2 mmol/L	7 985	149	578 (492-678)	0.97 (0.64-1.47)	866	14	600 (355-1013)	0.75 (0.32-1
32 Missing*	39 257	582	517 (477-561)		5 605	83	504 (406-625)	
33 Current daily sm	okers							
34 No	43 994	595	466 (430-505)	1.00	6 973	104	526 (434-638)	1.00
SO Yes	5 100	162	1038 (890-1211)	2.74 (2.30-3.27)	66	2	1090 (272-4357)	2.60 (0.64-1
Missing	0				0			

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

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Section/Topic	ltem #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-8
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-8
		(b) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-9
Data sources/	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe	5-9
measurement		comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	6-8,11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9-10
		(b) Describe any methods used to examine subgroups and interactions	9-10
		(c) Explain how missing data were addressed	10
		(d) If applicable, explain how loss to follow-up was addressed	10
		(e) Describe any sensitivity analyses	10
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed	11
		eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	We did not have
			information about
			reasons for non-
			participation in
			CONOR, but
			participation rates
			are given on page 7
			and the possibility of
			self-selection bias is
			discussed on page
			17. This was not
			relevant for the
			PREDICT cohort since
			it was based on
			contact with the
			primary health care.
		(c) Consider use of a flow diagram	Different persons
			were involved in the
			exclusion of
			participants, so it
			was easier to
			describe this process
			in text.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential	11-14
		confounders	
		(b) Indicate number of participants with missing data for each variable of interest	27-30 (Tables A1-A4
			in the appendices)
		(c) Summarise follow-up time (eg, average and total amount)	12-13 (Table 1)
Outcome data	15*	Report numbers of outcome events or summary measures over time	14

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Main results	16	(<i>a</i>) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15-16
		(b) Report category boundaries when continuous variables were categorized	13 (in table legend) and 26-29
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Sensitivity analyses are reported on page 15,17.
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-22
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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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

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Secondary Subject Heading:	Cardiovascular medicine, Public health
Keywords:	cardiovascular disease, risk factors, South Asians, ethnicity, prospective, cohort


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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

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Keywords: cardiovascular disease, risk factors, South Asians, ethnicity, prospective, cohort

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ABSTRACT

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

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

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

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Conclusion Differences in TC/HDL ratio and diabetes appear to explain some of the excess

risk of CVD in South Asians compared to Europeans. Preventing dyslipidaemia and diabetes

in South Asians may therefore help reduce their excess risk of CVD.

Strengths and limitations of this study

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

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INTRODUCTION

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

The mechanisms underlying the increased risk of CVD in South Asian populations are mostly unknown[1]. Few studies have examined the prospective relationship between CVD risk factors and subsequent CVD among South Asians[4, 7-9], despite the urgent need for such studies being addressed for more than ten years ago[10]. The two large and multinational case-control studies, Interheart[11] and Interstroke,[12] indicate that different populations share the same risk factors and that the relationship between risk factors and CVD is similar in different populations around the world. The Interheart study also concluded that the earlier age of AMI in South Asians can be largely attributed to higher risk factor levels at younger ages[13]. However, the Interheart and Interstroke studies are both case-control studies. In both Norway and New Zealand, South Asians have been found to have similar or higher mean total cholesterol (TC) to high density lipoprotein (HDL) ratio and higher prevalence of diabetes compared to the European majority populations[14-17]. However, they also have lower levels of smoking (especially women) and mean systolic blood pressure (SBP) than the European majority populations. Whether the higher risk of CVD among South

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Asians in Norway and New Zealand is due to higher levels of certain risk factors have not previously been studied.

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

MATERIAL AND METHODS

The New Zealand PREDICT-CVD cohort

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

The PREDICT software is used in around 35% of New Zealand primary care practices mainly in the Auckland and Northland regions, [19] which serve around 1.7 million people,

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representing around 37 % of the New Zealand population[20]. Any patient with their CVD risk assessed by a general practitioner (GP) or practice nurse into online PREDICT-CVD forms are included in the PREDICT cohort.

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

We used PREDICT data from August 2002 until September 2012. Members of the cohort were enrolled and examined continuously throughout this period via their contact with the primary health care. We included individuals aged 30 to 74 years since the dataset was comprised of people undergoing a risk assessment based on a Framingham risk score intended for people in this age group[22]. Using information from the GP, hospital discharges and medication dispensing, we excluded persons with a history of CVD (CHD (including angina), stroke, TIA, peripheral vascular disease (PVD), percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)), or atrial fibrillation at baseline (n=24 537), and people with overt renal disease, those who had eGFR \leq 29 and those with prior hospitalisations for congestive heart failure or who were on loop diuretics at baseline (n=1582). Only subjects with European or Indian background were included. The risk factor measurements in the PREDICT cohort were extracted from a standardised electronic template that primary care practitioners completed. The SBP was based on the mean of the last two recordings done by the GP or practice nurse, in most cases with a manual mercury sphygmomanometer. Blood lipid and glucose or HbA1c measurements were carried out in the community laboratories routinely used by general practitioners and smoking status and

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other risk factor data was measured using a standard questionnaire completed by a primary care practitioner.

Cohort of Norway

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

All CONOR surveys followed the same standard procedure for collection of data from selfadministered questionnaires, physical measurements and blood samples. The CONOR questionnaire provided information on self-reported diabetes, smoking, use of blood pressure and/or lipid lowering medication and family history of CVD. All participants attended a clinical examination and non-fasting venous blood samples were drawn. SBP was measured by an automatic device (DINAMAP, Criticon, Tampa, FL,USA) after 2 minutes of seated resting. Three recordings were made at 1-min intervals. For the analyses we used the average of the second and third SBP measurements. The blood samples were subsequently measured for total cholesterol (TC) and HDL cholesterol[23].

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

We included participants aged 30-74 years old at baseline (n=3 871 excluded) to ensure comparable samples between the Norwegian and New Zealand data. We excluded

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participants not born in Norway or South Asia (n=5651 excluded), pregnant women (n=197), and participants with prior CVD ((coronary heart disease (CHD), cerebrovascular disease, atherosclerotic disease, transient ischemic attack (TIA) and heart failure (HF)) (n=353) or atrial fibrillation (n=31) registered in the hospital data before screening.

Outcomes

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

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

Ethnicity

Ethnicity in the New Zealand PREDICT data was based on two sources: 1) the PREDICT template filled in by the GP and 2) the National Health Index dataset, both according to predefined categories. A prioritising algorithm was used to agree on one ethnicity in case of multiple ethnicities recorded (details can be found in a supplementary file entitled the VIEW

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Ethnicity Protocol). The system for coding ethnicity in New Zealand enables identification of Indian people, who account for approximately 90% of South Asian people living in New Zealand. The remaining South Asian ethnic groups are classified as part of the "Other Asian" ethnic group in national health data and so could not be included here. Indian people can include both immigrants and individuals who have been born in New Zealand with parents (or older generations) who have immigrated. The majority of this group are immigrants since 76.5% of the people who identified themselves with the Indian ethnic group in New Zealand in 2013 were born overseas[27].

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

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

Statistical analysis

Baseline characteristics are reported as mean values with standard deviations for continuous variables and fractions for categorical variables. We tested the differences between the ethnic groups adjusted for age by analysis of covariance. We used Cox regression models to

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

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

Ethics

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

RESULTS

Baseline characteristics

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

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

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

New Zealand cohort	N	len	Women			
	European	Indian	European	Indian		
N	63 319	9 997	49 094	7 039		
Age (years)	55.0 (9.3)	47.4 (9.7)	58.7 (8.7)	52.9 (8.5)		
Age range	30.0 - 74.0	30.0 - 74.0	30.0 - 74.0	30.0 - 74.0		
TC (mmol/L)	5.36 (1.1)	5.09 (1.1)	5.68 (1.1)	5.04 (1.0)		
HDL cholesterol (mmol/L	1.29 (0.4)	1.14 (0.3)	1.59 (0.5)	1.30 (0.3)		
LDL cholesterol (mmol/L)	3.3 (1.0)	2.9 (1.0)	3.4 (1.1)	2.8 (0.9)		
TC/HDL ratio	4.35 (1.3)	4.60 (1.3)	3.68 (1.1)	3.93 (1.1)		
SBP (mmHg)	131.5 (16.3)	125.3 (16.1)	131.6 (17.4)	126.1 (17.4)		
Diastolic blood pressure (mmHg)	80.5 (10.0)	79.1 (10.4)	78.8 (9.7)	77.4 (9.8)		
Hypertension [†] (%)	40	34	44	39		
Type 2 diabetes ^{\$} (%)	9	24	9	29		
Former smokers (%)	19	6	16	1		
Current smokers (%)	12	9	10	1		
Family history of CVD [§] (%)	12	8	15	10		
Antihypertensive treatment (%)	24	26	30	32		
Lipid lowering treatment (%)	18	27	18	27		
Follow-up time (years)	2.94 (2.3)	2.93 (2.0)	2.92 (2.3)	2.83 (1.9)		
Norwegian cohort	N	1en	w	omen		
	Norwegian	South Asian	Norwegian	South Asian		
N	6 385	1 239	8 015	967		
Age (years)	43.7 (11.2)	41.4 (7.8)	43.9 (10.9)	40.3 (7.9)		
Age range	30.0 - 70.1	30.0 - 67.8	30.0 - 74.9	30.0 - 65.5		
TC (mmol/L)	5.60 (1.1)	5.48 (1.0)	5.41 (1.0)	4.98 (0.9)		
HDL cholesterol (mmol/L	1.31 (0.3)	1.07 (0.2)	1.62 (0.4)	1.24 (0.3)		
TC/HDL ratio	4.55 (1.4)	5.33 (1.4)	3.52 (1.1)	4.22 (1.2)		
SBP (mmHg)	132.6 (14.4)	126.6 (13.2)	124.0 (15.7)	119.1 (15.6)		
Diastolic blood pressure (mmHg)	77.6 (10.8)	76.9 (9.8)	71.5 (10.3)	70.0 (10.1)		
Hypertension [†] (%)	30	22	19	16		
Diabetes (%)	1.6	8.6	1.4	10.9		
Former smokers (%)	28	16	26	2		
Current smokers (%)	26	25	31	1		
Family history of heart disease* (%)	33	24	37	27		
Family history of stroke [#] (%)	11	3	13	4		
Antihypertensive treatment (%)	6	8	6	9		
Lipid lowering treatment (%)	4	6	3	6		
Follow-up time (years)	8.44 (1.4)	7.65 (1.4)	8.54 (1.2)	7.88 (1.1)		

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

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

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

CVD events

During follow-up, we observed 2 654 CVD events among 129 446 individuals in the New Zealand cohort (378 874 person-years) and 743 new CVD events among the 16 606 individuals in the Norwegian cohort (139 470 person-years). The overall crude rates were 700 per 100 000 person-years in the New Zealand cohort and 533 per 100 000 person-years in the Norwegian cohort. Ethnic specific rates for men and women in the two cohorts are shown in table 2 and in the Appendices (tables A1-A4). Also crude rates and age-adjusted HRs of CVD by risk factors, ethnic groups, cohort and gender can be found in the Appendices.

Prospective associations between risk factors and CVD

Increasing age was significantly associated with risk of CVD in both ethnic groups in both cohorts (Table 2). The age effect was very similar within the countries for both ethnic groups

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

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

/ -										_
, 8 9 10	MEN	N events/N [*]	Crude rate/100 000 person- years (95% CI)	Age (one year)	SBP (10 mm/Hg)	DBP (10 mm/Hg)	TC/HDL ratio (one unit)	Diabetes (yes/no)	Current smoking (yes/no)	
11	New Zealand cohort			HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	
12	European men	1518/63316	815 (775-857)	1.07 (1.06-1.07)	1.15 (1.12-1.18)	1.16 (1.10-1.22)	1.20 (1.16-1.23)	1.92 (1.68-2.19)	2.29 (2.02-2.59)	
13	Indian men	273/9997	933 (828-1050)	1.06 (1.05-1.07)	1.05 (0.98-1.13)	1.02 (0.91-1.14)	1.08 (0.98-1.19)	1.72 (1.34-2.20)	1.45 (0.99-2.11)	
14 15	<i>Norwegian cohort</i> Norwegian men	379/6385	703 (636-778)	1.10 (1.09-1.11)	1.15 (1.08-1.22)	1.19 (1.08-1.30)	1.22 (1.15-1.30)	3.15 (2.14-4.65)	1.86 (1.51-2.29)	,
16 17	South Asian men	79/1239	833 (668-1039)	1.11 (1.08-1.14)	1.17 (1.01-1.35)	1.21 (0.97-1.51)	1.23 (1.05-1.42)	1.61 (0.90-2.86)	1.43 (0.88-2.30)	
18 19	WOMEN	N events/N [*]	Crude rate/100 000 person- years (95% CI)	Age (one year)	SBP(10 mm/Hg)	DBP (10 mm/Hg)	TC/HDL ratio (one unit)	Diabetes (yes/no)	Current smoking (yes/no)	
20	New Zealand cohort		,,	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	
21	European women	757/49094	528 (492-567)	1.06 (1.05-1.07)	1.09 (1.05-1.13)	1.13 (1.05-1.22)	1.14 (1.09-1.21)	1.93 (1.59-2.35)	2.74 (2.30-3.27)	
22	Indian women	106/7039	531 (439-643) 🧹	1.06 (1.03-1.08)	1.27 (1.16-1.39)	1.25 (1.03-1.50)	1.21 (1.03-1.41)	2.29 (1.55-3.37)	2.60 (0.64-10.59)	(
23 24	Norwegian cohort	259/8015	378 (335-427)	1 10 (1 09-1 12)	1 20 (1 12-1 28)	1 32 (1 18-1 //7)	1 30 (1 19-1 /3)	2 79 (1 52-5 11)	2 22 (1 73-2 84)	
25 26-	South Asian women	26/967	341 (232-501)	1.14 (1.09-1.19)	1.06 (0.86-1.30)	1.07 (0.74-1.55)	1.04 (0.77-1.39)	2.74 (1.21-6.22)	+	
20		The numbers of	at avants and near	alo included in the	analycac may dif	tor due to missing	rick tactor data	Four word miccing	in	

^{*}The numbers of events and people included in the analyses may differ due to missing risk factor data. Few were missing in the NZ cohort. [†] Not calculated due to no exposed cases.

DBP, diastolic blood pressure; HDL, high density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol.

Ethnic difference in CVD

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

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reduction in risk estimate after adjustment was among South Asian women in the New

Zealand cohort where the risk estimate was only reduced by 7 % (from 1.42 - 1.39).

Table 3. Hazard ratios (95% CI) for first CVD event in South Asian groups compared to ethnic European groups in New Zealand and Norway.

			Men		Women	
			Indian vs. European NZ	South Asians vs. Norwegians	Indian NZ vs. European NZ	South Asians vs. Norwegians
N events/N Adjusted for			1791/73308	436/7387	863/56126	264/8558
		Age	1.75 (1.53-2.00)	1.92 (1.48-2.49)	1.42 (1.16-1.75)	1.87 (1.21-2.87)
	Age, TC/	HDL ratio	1.77 (1.55-2.02)	1.66 (1.27-2.16)	1.41 (1.14-1.73)	1.52 (0.98-2.36)
	Age, TC/HDL ratio,	diabetes	1.49 (1.30-1.71)	1.42 (1.08-1.87)	1.15 (0.92-1.42)	1.30 (0.82-2.04)
	Age, TC/HDL ratio, diab	etes, SBP	1.57 (1.37-1.80)	1.53 (1.16-2.01)	1.19 (0.96-1.47)	1.31 (0.83-2.07)
	Age, TC/HDL ratio, diabetes, SBP,	smoking	1.64 (1.43-1.88)	1.57 (1.19-2.07)	1.39 (1.11-1.73)	1.76 (1.09-2.82)

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

Additional analyses showed that the excess risk in South Asians was particularly high for CHD. The full-adjusted HRs for CHD (corresponding to the analyses in the last row of Table 3) were 2.07; 95% CI 1.76-2.44 in South Asian men and 1.60; 95% CI 1.20-2.13 in South Asian women in New Zealand. In the Norwegian cohort, the full-adjusted HRs for CHD were 1.86; 95% CI 1.36-2.55 in South Asian men and 2.84; 95% CI 1.61-5.03 in South Asian women. In the sensitivity analyses for table 3 where we excluded people using BP- or lipid lowering medication at baseline, the patterns according to the risk factor adjustments remained the same as in the main analysis.

DISCUSSION

This study confirmed that the traditional risk factors SBP, TC/HDL ratio, diabetes and smoking are all positively associated with risk of CVD in South Asians as well as in Europeans. The present study also confirmed that South Asians had an increased risk of CVD compared

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to Europeans and that ethnic differences in the distribution of TC/HDL ratio and type 2 diabetes appear to explain some of this excess risk.

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

Strengths of the PREDICT cohort are the large sample size and the completeness of risk factors included in the risk-assessment. Only 0.01% were missing on any of the four major risk factors because they were part of the prediction algorithm and thereby compulsory to fill in to the PREDICT template. Furthermore, comprehensive national health registers were used to identify and exclude people with prior CVD and to determine cardiovascular outcomes. In the New Zealand cohort, some recruitment bias is likely since risk assessment was initially prioritized for high-risk patients. Indian patients are therefore over-represented in the cohort together with Maoris and Pacifics[19]. The representativeness of the source population is, however, improving as PREDICTs coverage increases. In this study, follow-up extended to 2012 when PREDICT included 50% of guideline-eligible patients in the practices where the PREDICT software is used[32]. We did not assume that the cohorts were representative of the general populations in the two countries, but that the ethnic groups within the two cohorts should be comparable. Adjusting for age was therefore particularly important in the New Zealand cohort since South Asians were around seven years younger than Europeans. Results from the two cohorts showed approximately the same regarding ethnic differences, which is a strength concerning the external validity of these results. A limitation in the New Zealand data is short follow-up time restricting the statistical power.

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Another limitation is the lack of standardized BP measurements since recorded BP can easily be affected by a range of factors including the type of device used[33].

Strengths of CONOR data are the standardized measurements of risk factors, the linkage with disease outcomes from comprehensive national health registers and the standardized way of defining ethnicity using country of birth. A validation study examining the Oslo Health study, showed that participants with a non-western background had a lower participation rate than others[34]. This may reflect self-selection which can work both ways; healthy and resourceful people have the energy and motivation to participate or less healthy people who think their health could benefit from participating do so. Self-selection is unlikely to influence associations between risk factors and subsequent disease, but could influence the ethnic comparisons if the mechanisms were systematically different for the ethnic groups. The South Asian group in the Norwegian cohort was relatively small, which reduced the precision of the estimates and limited the statistical power. Another limitation in the CONOR data is missing information on some of the risk factors (see tables A1-A2 in the appendices for numbers of missing). However, the extent of missing was small. The risk factor with most missing in CONOR was diabetes (3% for the total cohort).

In both cohorts, the endpoints are based on register data, including both hospital and mortality data, which enables almost complete ascertainment of CVD events. In New Zealand, more than 95% of patients with an acute CVD event are managed by governmentfunded health services[19]. However, CVD events occurring among participants who travelled outside of New Zealand, those who emigrated after the index CVD risk assessment or among participants treated in private hospitals would not be captured in the national hospital and mortality registers[19]. We have no information about possible emigration for

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the New Zealand cohort, but for the Norwegian cohort we know that few people have emigrated (about 1% of the ethnic Norwegians and <3% of the South Asians who participated in the Oslo health studies had emigrated by the end of follow-up). A limitation for both cohorts is also the lack of medication data during follow-up. However, adjustment for baseline medication did not change the estimates (results not shown), and Table 1 shows that South Asians used more antihypertensives and lipid lowering drugs at baseline than Europeans. Both countries have universal health care and South Asians should have the same access to cardiovascular medication as Europeans. It is therefore not likely that lack of treatment explains the differences in risk of CVD between the two ethnic groups.

Our finding that the traditional major CVD risk factors contribute to the development of CVD in South Asians as in Europeans was an expected, yet important, finding since most knowledge about CVD prevention is based on studies in populations of European descent, and some have questioned whether these risk factors apply worldwide[11, 35]. This finding is in line with the large INTERHEART and INTERSTROKE case-control studies[11, 12], which reported that 90% of the population attributable risk for AMI and stroke worldwide was accounted for by respectively nine and ten (similar) risk factors, including those included in the present study. We are only aware of two other prospective studies reporting HRs for the prospective relationship between major CVD risk factors and subsequent CVD in South Asians [7, 36]. One of these studies included only men, [7] and the other showed estimates for men and women combined and did not include blood lipids[36]. These studies generally agree with our findings that traditional risk factors contribute to the development of CVD in South Asians as in Europeans [7, 36]. Also, consistent with previous reports [5, 6], we found that South Asians in both Norway and New Zealand have a higher risk of CVD compared to the European majority populations. By including all the measured risk factors (BP, TC/HDL

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

The excess risk of CVD among South Asians compared to Europeans in the Norwegian cohort was almost two-fold. This is comparable to what we reported previously when studying the total Norwegian population[5]. The South Asians in the New Zealand cohort had 42-75% higher risk of CVD compared to European New Zealanders which also agrees with previous New Zealand studies [6]. In both the Norwegian and New Zealand data, South Asians had higher baseline levels of dyslipidemia indicated by the TC/HDL ratio and higher diabetes prevalence compared to the European majority populations, which is in general agreement with previous knowledge from these countries[14-16]. Attenuation of the excess risk in South Asians versus Europeans was best achieved in the Cox model only including diabetes and TC/HDL ratio as covariates in addition to age. The same was found in both cohorts, clearly indicating that the unfavorable distribution of blood lipids and type 2 diabetes explains some of the higher risk of CVD in South Asians. South Asians generally have a high prevalence of metabolic risk factors related to insulin resistance, often clustered so that they match the concept of the metabolic syndrome[37-40]. A British cohort study that tested whether traditional risk factors could account for the high mortality of CHD among South Asian men compared to European men, reported that adjusting for insulin resistance, dyslipidemia and hyperglycemia in South Asians did not explain their higher risk[7]. However, they also adjusted for smoking and total cholesterol, which were both less prevalent/lower among South Asian men compared to European men.

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It is unclear why the traditional risk factors do not completely explain the excess risk of CVD in South Asians. This could be related to incomplete adjustments; due to either imprecise measurement of risk factors or that other important risk factors were not included (e.g. waist measurement, length of time since diabetes diagnosis). A number of non-conventional risk factors are also thought to partially account for the high risk of CVD in South Asians, including dysfunctional HDL, C-Reactive Protein, thrombogenic risk factors, telomere length, high homocysteine levels and low birth weight[41, 42]. Socioeconomic factors could probably also explain some of the differences in risk between the ethnic groups, but we did not have such variables. Another possibility is that risk factors work cumulatively over time in the development of atherosclerosis, and some risk factors may also work at specific and crucial time points during the life course. Measurements taken on single occasions may also lead to an underestimation of the strength between the *usual* levels of the risk factors and later disease, known as the regression dilution bias[43]. Consequently, it is unlikely that the ethnic differences would disappear completely by adjusting for selected risk factors measured once in midlife.

Although South Asians seem to have an underlying susceptibility for metabolic diseases, traditional and modifiable risk factors are important for preventing disease. Our analyses indicate that it is important to focus on the prevention of type 2 diabetes and dyslipidaemia when aiming to reduce the burden of CVD among South Asians. The additional effect of abdominal obesity for the risk of CVD among South Asians in Norway and New Zealand has, however, not yet been studied although we know that the prevalence is high in this ethnic group[38, 44]. In both Norway[45, 46] and New Zealand,[47] intervention studies targeting immigrants from South Asia have been carried out with some promising results. A UK-study that prospectively examined the influence from four health behaviors on the risk of CVD in

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South Asian immigrants and UK Europeans found an important potential for disease prevention among South Asians if they adhered to healthy behaviors[8].

CONCLUSION

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

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VIEW Ethnicity Protocol

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

Table 1

Level 2 ethnic codes

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

VIEW Ethnicity December 2015

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PREDICT 2015 baseline data – Unique ethnicity codes

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

Source	Variable name	Eth	nici	ty Co	odes	;								
		10	11	12	2′	1 3	30	31	32	33	34	35	36	37
	pt_ethnic_group_1	40	41	42	43	3 4	14	51	52	53	54	441	44	12
		443	44	4 4	441 [·]	14	4412	2 4	4413	444	14	444′	15 I	NA
		10	11	12	2'	1 3	30	31	32	33	34	35	36	5 37
PREDICT 2015	pt_ethnic_group_2	40	41	42	43	3 4	14	51	52	53	54	99	44	1
		443	44	411	444	412	444	414	NA					
		10	11	12	2	1 3	30	31	32	33	34	35	36	5 37
	pt_ethnic_group_3	40	41	42	4	3 4	14	51	52	53	54	99	44	1
		444	11	444	14	NA	04		00	0.4	05	00	07	40
	nhi_ethnicg1	10	11	12	21	30 51	31	32 52	33 54	34 61	35	30	37	40
		41	42	43	44 01	20	21	23	22	24	94	90	37	99 40
Ministry of	nhi_ethnicg2	10	12	12	ΖI ΛΛ	50	52	32 53	53 51	54 61	35 Q/	30 05	37 07	40 00
Health 2015		NA	72	73		51	52	00	54	01	54	55	57	55
		10	11	12	21	30	31	32	33	34	35	36	37	40
	nhi_ethnicg3		42	43	44	51	52	53	61	97	99	NA	•	
NB: There are no	NAs in "nhi_ethnicg1"													

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

Procedure for Ethnicity Allocation

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

1) Is this person Maori? If yes, write "NZMaori", otherwise next question.

2) Is this person Pacific? If yes, write "Pacific", otherwise next question.

3) Is this person Indian? If yes, write "Indian", otherwise next question.

4) Is this person Chinese? If yes, write "Chinese", otherwise next question.

5) Is this person Asian? If yes, write "Asian", otherwise next question.

6) Is this person MELAA? If yes, write "MELAA", otherwise next question.

7) Is this person Other? If yes, write "Other", otherwise next question.

8) Is this person European? If yes, write "European", otherwise next question.

9) Is the ethnicity unknown, not answered, not identifiable? If yes, write "No_not_stated".

NB: MELAA = Middle Eastern, Latin American, African

VIEW REVISED Procedure for Ethnicity Allocation

1) Is this person Maori? If yes, write "NZMaori", otherwise next question.

2) Is this person Pacific? If yes, write "Pacific", otherwise next question.

3) Is this person Indian? If yes, write "Indian", otherwise next question.

4) Is this person Chinese? If yes, write "Chinese", otherwise next question.

5) Is this person Asian? If yes, write "Asian", otherwise next question.

6) Is this person European? If yes, write "European", otherwise next question.

7) Is this person MELAA? If yes, write "MELAA", otherwise next question.

8) Is this person Other? If yes, write "Other", otherwise next question.

9) Is the ethnicity unknown, not answered, not identifiable? If yes, write "No_not_stated".



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Multiple Ethnicities

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

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

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

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

The use of "OTHER" Ethnicity

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

Original "ag_eth" Classification

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

Problems with above coding convention:

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

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

Frequency

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

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

Proportion

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

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NEW "view_ag_eth" Classification

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

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

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

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

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

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

Frequency

Asian	Chinese	European	Indian	MELAA	No_not_stated	NZMaori
18745	26563	276433	39205	6797	654	62181
Other	Pacific	<na></na>				
2262	59305	0				
Proport	ion					
Asian	Chinese	European	Indian	MELAA	No_not_stated	NZMaori
0.038	0.054	0.562	0.080	0.014	0.001	0.126
Other	Pacific	<na></na>				
0.005	0.121	0.000				

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Appendix A

Prioritisation Output for Ethnicity

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

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

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

Limitations are that prioritised output:

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

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

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Appendix							-016819 on ht, includin			
Table A1. Crude rates	and age-adjus	ted HR of CV	D by risk factors, Nor	wegian and South	n Asian men fror	n the Nor	Wegian cohort.			
	Norwegian						S C C C C C C C C C C C C C C C C C C C			
	No. of persons	No. of CVD events	Crude rate/100 000 person-years (95% CI)	HR (95% CI)	No. of persons	No. of CV events	eiginer aber Defer Here Here Here Son-years (95% CI)	HR (95% CI)		
Total	6385	379	703 (636-778)		1239	79	c 339 (668-1039)			
Diabetes							Sup			
No	6167	339	649 (583-721)	1.00	1088	59	a) (545-908)	1.00		
Yes	101	28	3936 (2718-5701)	3.15 (2.14-4.65)	103	16	a a 18 6 (1327-3536)	1.61 (0.90-2.86)		
Missing	117	12	539 (298-973)		48	4	a 1 (416-2956)			
SBP							BE			
<140	4701	198	493 (429-566)	1.00	1068	56	2.983 (525-886)	1.00		
140-159	1373	130	1150 (969-1366)	1.39 (1.10-1.74)	150	19	بَقْ 1(1072-2636)	1.44 (0.83-2.49)		
>160	296	51	2228 (1693-2932)	1.76 (1.28-2.42)	21	4	≥ 2855 (1075-7634)	1.51 (0.53-4.28)		
Missing	15	0			0	0	njo tra			
TC/HDL ratio							inir <mark>pe</mark>			
<5	4284	207	568 (495-650)	1.00	538	21	ૡ 4 🙀 (325-765)	1.00		
≥5	2090	170	980 (843-1139)	1.64 (1.34-2.00)	698	58	a 1 4 5 (854-1430)	2.14 (1.30-3.52)		
Missing	11	2	2328 (582-9307)		3	0	d cor			
тс										
< 5 mmol/L	1930	68	410 (324-520)	1.00	407	19	<mark>ຊ</mark> 60 (389-955)	1.00		
≥ 5 mmol/L	4444	309	830 (742-927)	1.17 (0.90-1.53)	830	60	စ္တံ 94၌ (734-1217)	1.49 (0.89-2.49)		
Missing	11	2	2328 (582-9307)		2	0	:hn			
HDL							olc 12,			
< 1.00 mmol/L	1032	78	915 (733-1142)	1.00	525	34	. 85 (611-1197)	1.00		
≥1.00 mmol/L	5343	299	660 (589-739)	0.61 (0.47-0.78)	711	45	بة 82 4 (613-1099)	0.99 (0.63-1.55)		
Missing	10	2	2608 (652-10427)		3	0	at /			
Current daily smokers							ge			
No	4706	231	578 (508-657)	1.00	905	52	74 🦉 (571-983)	1.00		
Yes	1660	146	1062 (903-1248)	1.86 (1.51-2.29)	302	25	10888 (735-1610)	1.43 (0.88-2.30)		
Missing	19	2	1236 (309-4941)		32	2	83 (208-3323)			

Cl, confidence interval; CVD, cardiovascular disease; HDL, high density lipoprotein; HR, hazard ratio: TC, total cholesterol; SBP, systolic blood propaging For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtmge

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APPENDIX Table A2. Crude rates and age-adjusted HR of CVD by risk factors, Norwegian and South Asian women from the Nerwegian cohort.

	Norwegian				South Asian		eco	
	No. of	No. of CVD	Crude rate/100 000	HR (95% CI)	No. of	No. of CVI	SET THE SECONDERSON OF THE SECO	
Total	8015	259	378 (335-427)		967	26	te e 3 41 (232-501)	
Diabetes			, , , , , , , , , , , , , , , , , , ,				id te	
No	7657	237	361 (318-410)	1.00	816	17	a b c c c c c c c c c c	
Yes	105	11	1305 (723-2356)	2.79 (1.52-5.11)	100	9	2.74 (1.21-6.22) 2.74 (1.21-6.22	<u>'</u>)
Missing	253	11	539 (298-973)	· · · ·	51	0	anc	,
SBP							l dar	
<140	6823	151	257 (219-302)	1.00	876	18	a b b c (164-412) 1.00	
140-159	920	76	999 (798-1251)	1.82 (1.37-2.43)	67	4	1.45 (0.48-4.34)
>160	266	31	1450 (1020-2062)	2.11 (1.42-3.15)	23	4	1. 3 3 78 (892-6335) 2.42 (0.76-7.71	.)
Missing	6	1	2128 (300-15106)		1	0		
TC/HDL ratio								
<5	7225	203	328 (286-376)	1.00	749	17	a b 87 (178-462) 1.00	
≥ 5	781	54	833 (638-1088)	1.79 (1.33-2.42)	215	9 9	2 37 (279-1032) 1.46 (0.65-3.30))
Missing	9	2	3122 (781-12483)			0	an <u>a</u>	
тс								
< 5 mmol/L	3004	44	169 (125-227)	1.00	524	8	1 .00 1 .00	
≥ 5 mmol/L	5002	213	503 (440-576)	1.40 (1.00-1.97)	440	18	a 321 (328-826) 1.54 (0.65-3.64	•)
Missing	9	2	3122 (781-12483)		3	0	tec	
HDL							hn e 1	
< 1.2 mmol/L	1057	52	587 (447-770)	1.00	465	12	3 29 (187-578) 1.00	
≥1.2 mmol/L	6949	205	344 (300-395)	0.55 (0.40-0.74)	499	14	6 6 6 6 6 6 6 7 7 6 6 7 7 6 7 7 7 7 7 7 1 1 1 1 1 1 1 1 1 1	<i>!</i>)
Missing	9	2	3122 (781-12483)		3	0		
Current daily smokers							t Aç	
No	5461	134	285 (241-338)	1.00	883	24	9 44 (231-514) 1.00	
Yes	2510	119	564 (471-675)	2.22 (1.73-2.84)	13	0	Ce	
Missing	44	6	1759 (790-3916)		71	2	00 3 65 (91-1461)	

CI, confidence interval; CVD, cardiovascular disease; HDL, high density lipoprotein; HR, hazard ratio: TC, total cholesterol; SBP, systolic blood prossure For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtmg

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APPENDIX

		European						
							n 6 E	
	No. of	No. of CVD	Crude rate/100 000	HR (95% CI)	No. of persons	No. of CVD	Crude Pate/ 00 000	HR (95% CI)
	persons	events	person-years (95% CI)			events	person () ဟြ ချို (95% Cl)	
Total	63 319	1 518	815 (775-857)		9 997	273	933 (828 4 05 0)	
Type 2 diabetes							gn elat	
No	57 760	1 241	728 (689-770)	1.00	7 641	158	712 (6 🗓 🛱 式)	1.00
Yes	5 559	277	1739 (1546-1957)	1.92 (1.68-2.19)	2 356	115	1622 (සි 🛱 ජු 947)	1.72 (1.34-2.20
Missing	0				0		te) te)	
SBP							t a nio	
<140	42 666	776	632 (589-678)	1.00	7 888	188	805 (6 3 3 3 4 4)	1.00
140-159	16 417	514	1030 (945-1123)	1.35 (1.20-1.51)	1 723	68	1431 (ដ្ឋាភ័និ 4 814)	1.37 (1.03-1.82
>160	4 236	228	1675 (1471-1908)	2.03 (1.75-2.36)	386	17	1462 (90 92 2 3 52)	1.22 (0.74-2.02
Missing	0				0			
TC/HDL ratio							s)	
<5	45 177	994	756 (711-805)	1.00	6 379	178	926 (799-1022)	1.00
≥5	18 139	524	955 (876-1040)	1.58 (1.42-1.76)	3 617	95	946 (7 🛱 - 1 🍒 7)	1.28 (1.00-1.65
Missing*	3	0			1	0	raii	
тс							lin en	
< 5 mmol/L	20 226	395	879 (797-970)	1.00	4 450	103	841 (6 9 3-10 <mark>3</mark> 0)	1.00
≥ 5 mmol/L	36 071	684	756 (702-815)	1.01 (0.89-1.14)	5 130	137	974 (824-152)	1.36 (1.05-1.76
Missing*	7 022	439	861 (785-946)		417	33	1114 (2 92-1 <mark>3</mark> 67)	
HDL								
< 1.00 mmol/L	2 325	55	986 (757-1284)	1.00	561	15	1327 (800-2202)	1.00
≥1.00 mmol/L	10 920	323	891 (799-993)	0.87 (0.66-1.17)	1 231	39	1140 (833-1561)	0.62 (0.33-1.14
Missing*	50 074	1 140	789 (744-836)	. ,	8 205	219	886 (7 26-1011)	·
Current daily smokers							0 0	
No	55 587	1 197	733 (692-776)	1.00	9 105	242	913 (8 6 5-10 8 5)	1.00
Yes	7 731	321	1396 (1252-1558)	2.29 (2.02-2.59)	892	31	1123 (7 90-1 5 97)	1.45 (0.99-2.1
Missina	1	0	. ,	. ,	0		it /	

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

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APPENDIX Table A4. Crude rates and age-adjusted HR of CVD by risk factors, European and Indian New Zealand women from the New Zealand cohort.

European				Indian di on			
				6 E			
No. of persons	No. of CVD events	Crude rate/100 000	HR	No. of persons of	No. of CVD	Crude rate/100 000	HR
		person-years (95% CI)		JS E M	events	person-years (95% CI)	
49 094	757	528 (492-567)		7 039 ö ö ö	106	531 (439-643)	
				ela ela			
44 880	635	485 (448-524)	1.00	5 010 tean 7	50	358 (271-472)	1.00
4 214	122	994 (832-1187)	1.93 (1.59-2.35)	2 029 6 5 0	56	936 (720-1216)	2.29 (1.55-3.3
0				0 te Several S			
				t anlo			
32 178	395	436 (395-481)	1.00	5 370 n eide	56	371 (285-482)	1.00
13 019	258	646 (572-730)	1.22 (1.04-1.44)	1 281 da 4	34	919 (656-1286)	2.11 (1.37-3.2
3 896	104	813 (671-985)	1.42 (1.14-1.77)	388 a A F	16	1388 (851-2266)	2.99 (1.70-5.2
1	0			0 nin ES			
				ing (ttp			
42 800	626	507 (469-549)	1.00	5 895 🛓 💆	89	527 (428-648)	1.00
6 289	131	658 (555-781)	1.42 (1.17-1.71)	1 143 🚡 🛃	17	559 (347-898)	1.11 (0.66-1.8
5	0				0		
				ng, <mark>n.</mark> b			
10 940	127	515 (433-613)	1.00	3 277 a 🤁	57	639 (493-828)	1.00
32 974	415	516 (469-569)	0.96 (0.79-1.17)	3 515 🙍 😋	37	398 (289-550)	0.62 (0.41-0.9
5 180	215	561 (491-641)		247 m 2	12	689 (391-1212)	
				lar on			
1 852	26	529 (360-776)	1.00	568 tec Jun	9	781 (406-1501)	1.00
7 985	149	578 (492-678)	0.97 (0.64-1.47)	866 hn e 1	_ 14	600 (355-1013)	0.75 (0.32-1.7
39 257	582	517 (477-561)	, ,	5 605 0 N	83	504 (406-625)	,
		· · · ·		gie:		, ,	
43 994	595	466 (430-505)	1.00	<u>ທ່</u> ດ 6973 ຍ	104	526 (434-638)	1.00
5 100	162	1038 (890-1211)	2.74 (2.30-3.27)	66	2	1090 (272-4357)	2.60 (0.64-10
0				o ger	-	1000 (272 1007)	2.00 (0.04 10
	European No. of persons 49 094 44 880 4 214 0 32 178 13 019 3 896 1 42 800 6 289 5 10 940 32 974 5 180 1 852 7 985 39 257 43 994 5 100 0	European No. of persons No. of CVD events 49 094 757 44 880 635 4 214 122 0 122 32 178 395 13 019 258 3 896 104 1 0 42 800 626 6 289 131 5 0 10 940 127 32 974 415 5 180 215 1 852 26 7 985 149 39 257 582 43 994 595 5 100 162	EuropeanNo. of personsNo. of CVD eventsCrude rate/100 000 person-years (95% Cl)49 094757528 (492-567)44 880635485 (448-524)4 214122994 (832-1187)0 0 32178 39532 178395436 (395-481)13 019258646 (572-730)3 896104813 (671-985)1 0 0 42 800626507 (469-549)6 289131658 (555-781) 5 0 10 940127515 (433-613)32 974415516 (469-569) $5 180$ 215561 (491-641)1 85226529 (360-776) $7 985$ 149578 (492-678) $39 257$ 582 $517 (477-561)$ 43 994595466 (430-505) $5 100$ 1621038 (890-1211)	EuropeanNo. of personsNo. of CVD eventsCrude rate/100 000 person-years (95% Cl)HR49 094757528 (492-567)HR44 880635485 (448-524)1.004 214122994 (832-1187)1.93 (1.59-2.35)01.0032 178395436 (395-481)1.0013 019258646 (572-730)1.22 (1.04-1.44)3 896104813 (671-985)1.42 (1.14-1.77)1042 800626507 (469-549)1.006 289131658 (555-781)1.42 (1.17-1.71)5010 940127515 (433-613)1.0032 974415516 (469-569)0.96 (0.79-1.17)5 180215561 (491-641)1 85226529 (360-776)1.007 985149578 (492-678)0.97 (0.64-1.47)39 257582517 (477-561)43 994595466 (430-505)1.005 1001621038 (890-1211)2.74 (2.30-3.27)	European Indian Indian No. of persons No. of CVD events Crude rate/100 000 person-years (95% CI) HR No. of persons For Engineer 2017, Downloaded to rectrant downloaded 49 094 757 528 (492-567) 7 039 For Engineer 2017, Downloaded 44 880 635 485 (448-524) 1.00 5 010 for extrant downloaded 42 14 122 994 (832-1187) 1.93 (1.59-2.35) 2 029 0 32 178 395 436 (395-481) 1.00 5 370 0 31 019 258 646 (572-730) 1.22 (1.04-1.44) 1 281 fater mining, and similar technologies. 1 0 0 0 0 0 0 42 800 626 507 (469-549) 1.00 5 895 1 6 289 131 658 (555-781) 1.42 (1.17-1.71) 1 143 3 2974 415 516 (469-569) 0.96 (0.79-1.17) 3 515 7 985 149 578 (492-678) 0.97 (0.64-1.47) 866 39 257	Indian di Indian di 	$ \begin{array}{c c c c c c c c c c c c c c c c c c c $

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

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

Section/Topic	ltem #	Recommendation	Reported on page #
Title and abstract1(a) Indicate the study's design with a		(a) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-8
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-8
		(b) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-9
Data sources/	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe	
measurement		comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	6-8,11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9-10
		(b) Describe any methods used to examine subgroups and interactions	9-10
		(c) Explain how missing data were addressed	10
		(d) If applicable, explain how loss to follow-up was addressed	10
		(e) Describe any sensitivity analyses	10
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study-eg numbers potentially eligible, examined for eligibility, confirmed	11
		eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	We did not have
			information about
			reasons for non-
			participation in
			CONOR, but
			participation rates
			are given on page 7
			and the possibility of
			self-selection bias is
			discussed on page
			18. This was not
			relevant for the
			PREDICT cohort since
			it was based on
			contact with the
			primary health care.
		(c) Consider use of a flow diagram	Different persons
			were involved in the
			exclusion of
			participants, so it
			was easier to
			describe this process
			in text.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential	11-13
		(b) Indicate number of participants with missing data for each variable of interest	Tables A1 A4 in the
			annendices
		(c) Summarise follow-up time (eg. average and total amount)	12 (Table 1)
Outcomo data	15*	Report numbers of outcome events or summary measures over time	
Outcome data	15*	Report numbers of outcome events of summary measures over time	13

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Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence	15-16
		interval). Make clear which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	12 (in table legend)
			and 26-29
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Sensitivity analyses
			are reported on page
			14, 16
Discussion			
Key results	18	Summarise key results with reference to study objectives	16-17
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from	16-22
		similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on	23
		which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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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

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Primary Subject Heading :	Epidemiology
Secondary Subject Heading:	Cardiovascular medicine, Public health
Keywords:	cardiovascular disease, risk factors, South Asians, ethnicity, prospective, cohort



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

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Wordcount, abstract: 298 Wordcount, manuscript text: 4660

Keywords: cardiovascular disease, risk factors, South Asians, ethnicity, prospective, cohort

ABSTRACT

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

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

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

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Conclusion Differences in TC/HDL ratio and diabetes appear to explain some of the excess

risk of CVD in South Asians compared to Europeans. Preventing dyslipidaemia and diabetes

in South Asians may therefore help reduce their excess risk of CVD.

Strengths and limitations of this study

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

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INTRODUCTION

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

The mechanisms underlying the increased risk of CVD in South Asian populations are mostly unknown[1]. Few studies have examined the prospective relationship between CVD risk factors and subsequent CVD among South Asians[4, 7-9], despite the urgent need for such studies being addressed for more than ten years ago[10]. The two large and multinational case-control studies, Interheart[11] and Interstroke,[12] indicate that different populations share the same risk factors and that the relationship between risk factors and CVD is similar in different populations around the world. The Interheart study also concluded that the earlier age of AMI in South Asians can be largely attributed to higher risk factor levels at younger ages[13]. However, the Interheart and Interstroke studies are both case-control studies. In both Norway and New Zealand, South Asians have been found to have similar or higher mean total cholesterol (TC) to high density lipoprotein (HDL) ratio and higher prevalence of diabetes compared to the European majority populations[14-17]. However, they also have lower levels of smoking (especially women) and mean systolic blood pressure (SBP) than the European majority populations. Whether the higher risk of CVD among South

Asians in Norway and New Zealand is due to higher levels of certain risk factors have not previously been studied.

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

MATERIAL AND METHODS

The New Zealand PREDICT-CVD cohort

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

The PREDICT software is used in around 35% of New Zealand primary care practices mainly in the Auckland and Northland regions, [19] which serve around 1.7 million people,

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representing around 37 % of the New Zealand population[20]. Any patient with their CVD risk assessed by a general practitioner (GP) or practice nurse into online PREDICT-CVD forms are included in the PREDICT cohort.

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

We used PREDICT data from August 2002 until September 2012. Members of the cohort were enrolled and examined continuously throughout this period via their contact with the primary health care. We included individuals aged 30 to 74 years since the dataset was comprised of people undergoing a risk assessment based on a Framingham risk score intended for people in this age group[22]. Using information from the GP, hospital discharges and medication dispensing, we excluded persons with a history of CVD (CHD (including angina), stroke, TIA, peripheral vascular disease (PVD), percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)), or atrial fibrillation at baseline (n=24 537), and people with overt renal disease, those who had eGFR \leq 29 and those with prior hospitalisations for congestive heart failure or who were on loop diuretics at baseline (n=1582). Only subjects with European or Indian background were included. The risk factor measurements in the PREDICT cohort were extracted from a standardised electronic template that primary care practitioners completed. The SBP was based on the mean of the last two recordings done by the GP or practice nurse, in most cases with a manual mercury sphygmomanometer. Blood lipid and glucose or HbA1c measurements were carried out in the community laboratories routinely used by general practitioners and smoking status and

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other risk factor data was measured using a standard questionnaire completed by a primary care practitioner.

Cohort of Norway

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

All CONOR surveys followed the same standard procedure for collection of data from selfadministered questionnaires, physical measurements and blood samples. The CONOR questionnaire provided information on self-reported diabetes, smoking, use of blood pressure and/or lipid lowering medication and family history of CVD. All participants attended a clinical examination and non-fasting venous blood samples were drawn. SBP was measured by an automatic device (DINAMAP, Criticon, Tampa, FL,USA) after 2 minutes of seated resting. Three recordings were made at 1-min intervals. For the analyses we used the average of the second and third SBP measurements. The blood samples were subsequently measured for total cholesterol (TC) and HDL cholesterol[23].

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

We included participants aged 30-74 years old at baseline (n=3 871 excluded) to ensure comparable samples between the Norwegian and New Zealand data. We excluded

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participants not born in Norway or South Asia (n=5651 excluded), pregnant women (n=197), and participants with prior CVD ((coronary heart disease (CHD), cerebrovascular disease, atherosclerotic disease, transient ischemic attack (TIA) and heart failure (HF)) (n=353) or atrial fibrillation (n=31) registered in the hospital data before screening.

Outcomes

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

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

Ethnicity

Ethnicity in the New Zealand PREDICT data was based on two sources: 1) the PREDICT template filled in by the GP and 2) the National Health Index dataset, both according to predefined categories. A prioritising algorithm was used to agree on one ethnicity in case of multiple ethnicities recorded (details can be found in a supplementary file entitled the VIEW

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Ethnicity Protocol). The system for coding ethnicity in New Zealand enables identification of Indian people, who account for approximately 90% of South Asian people living in New Zealand. The remaining South Asian ethnic groups are classified as part of the "Other Asian" ethnic group in national health data and so could not be included here. Indian people can include both immigrants and individuals who have been born in New Zealand with parents (or older generations) who have immigrated. The majority of this group are immigrants since 76.5% of the people who identified themselves with the Indian ethnic group in New Zealand in 2013 were born overseas[27].

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

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

Statistical analysis

Baseline characteristics are reported as mean values with standard deviations for continuous variables and fractions for categorical variables. We tested the differences between the ethnic groups adjusted for age by analysis of covariance. We used Cox regression models to

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

To check whether the use of BP medication at baseline would impact the analyses where SBP were included, we repeated the Cox regression analyses excluding people using antihypertensive medication at baseline. Correspondingly, we also repeated the Coxregression analyses for TC/HDL ratio without people using lipid lowering medication at baseline. In addition, since excluding those at highest risk could potentially impact the sensitivity analyses, we also adjusted for medication use without excluding anyone from the analyses (Tables A3-A4 in the Appendices).

Ethics

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

RESULTS

Baseline characteristics

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

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

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

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New Zealand cohort	Men		W	/omen
	European	Indian	European	Indian
N	63 319	9 997	49 094	7 039
Age (years)	55.0 (9.3)	47.4 (9.7)	58.7 (8.7)	52.9 (8.5)
Age range	30.0 - 74.0	30.0 - 74.0	30.0 - 74.0	30.0 - 74.0
TC (mmol/L)	5.36 (1.1)	5.09 (1.1)	5.68 (1.1)	5.04 (1.0)
HDL cholesterol (mmol/L	1.29 (0.4)	1.14 (0.3)	1.59 (0.5)	1.30 (0.3)
LDL cholesterol (mmol/L)	3.3 (1.0)	2.9 (1.0)	3.4 (1.1)	2.8 (0.9)
TC/HDL ratio	4.35 (1.3)	4.60 (1.3)	3.68 (1.1)	3.93 (1.1)
SBP (mmHg)	131.5 (16.3)	125.3 (16.1)	131.6 (17.4)	126.1 (17.4)
Diastolic blood pressure (mmHg)	80.5 (10.0)	79.1 (10.4)	78.8 (9.7)	77.4 (9.8)
Hypertension ⁺ (%)	40	34	44	39
Type 2 diabetes ^{\$} (%)	9	24	9	29
Former smokers (%)	19	6	16	1
Current smokers (%)	12	9	10	1
Family history of CVD [§] (%)	12	8	15	10
Antihypertensive treatment (%)	24	26	30	32
Lipid lowering treatment (%)	18	27	18	27
Follow-up time (years)	2.94 (2.3)	2.93 (2.0)	2.92 (2.3)	2.83 (1.9)
Norwegian cohort	Γ	Men	v	/omen
	Norwegian	South Asian	Norwegian	South Asian
N	6 385	1 239	8 015	967
Age (years)	43.7 (11.2)	41.4 (7.8)	43.9 (10.9)	40.3 (7.9)
Age range	30.0 - 70.1	30.0 - 67.8	30.0 - 74.9	30.0 - 65.5
TC (mmol/L)	5.60 (1.1)	5.48 (1.0)	5.41 (1.0)	4.98 (0.9)
HDL cholesterol (mmol/L	1.31 (0.3)	1.07 (0.2)	1.62 (0.4)	1.24 (0.3)
TC/HDL ratio	4.55 (1.4)	5.33 (1.4)	3.52 (1.1)	4.22 (1.2)
SBP (mmHg)	132.6 (14.4)	126.6 (13.2)	124.0 (15.7)	119.1 (15.6)
Diastolic blood pressure (mmHg)	77.6 (10.8)	76.9 (9.8)	71.5 (10.3)	70.0 (10.1)
Hypertension [†] (%)	30	22	19	16
Diabetes (%)	1.6	8.6	1.4	10.9
Former smokers (%)	28	16	26	2
Current smokers (%)	26	25	31	1
Family history of heart disease* (%)	33	24	37	27
Family history of stroke [#] (%)	11	3	13	4
Antihypertensive treatment (%)	6	8	6	9
Lipid lowering treatment (%)	4	6	3	6
Follow-up time (years)	8.44 (1.4)	7.65 (1.4)	8.54 (1.2)	7.88 (1.1)

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

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

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

CVD events

During follow-up, we observed 2 654 CVD events among 129 446 individuals in the New Zealand cohort (378 874 person-years) and 743 new CVD events among the 16 606 individuals in the Norwegian cohort (139 470 person-years). The overall crude rates were 700 per 100 000 person-years in the New Zealand cohort and 533 per 100 000 person-years in the Norwegian cohort. Ethnic specific rates for men and women in the two cohorts are shown in table 2 and in the Appendices (Tables A5-A8). Also crude rates and age-adjusted HRs of CVD by risk factors, ethnic groups, cohort and gender can be found in the same tables in the Appendices.

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Prospective associations between risk factors and CVD

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

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

11.									
12 13 14	MEN	N events/N [*]	Crude rate/100 000 person-	Age (one year)	SBP (10 mm/Hg)	DBP (10 mm/Hg)	TC/HDL ratio (one unit)	Diabetes (yes/no)	Current smoking (yes/no)
15	New Zealand		years (55% cl)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
16	cohort			. ,	. ,	. ,	. ,	. ,	. ,
17	European men	1518/63316	815 (775-857)	1.07 (1.06-1.07)	1.15 (1.12-1.18)	1.16 (1.10-1.22)	1.20 (1.16-1.23)	1.92 (1.68-2.19)	2.29 (2.02-2.59)
17	Indian men	273/9997	933 (828-1050)	1.06 (1.05-1.07)	1.05 (0.98-1.13)	1.02 (0.91-1.14)	1.08 (0.98-1.19)	1.72 (1.34-2.20)	1.45 (0.99-2.11)
18									
19	Norwegian conort	270/0205	702 (626 770)	1 10 (1 00 1 11)	1 15 (1 00 1 22)	1 10 /1 08 1 20)	1 22 /1 15 1 20)		1 96 /1 51 2 20)
20	Norwegian men	3/9/0385	/03 (030-//8)	1.10 (1.09-1.11)	1.15 (1.08-1.22)	1.19 (1.08-1.30)	1.22 (1.15-1.30)	3.15 (2.14-4.05)	1.80 (1.51-2.29)
21	South Asian men	/9/1239	833 (668-1039)	1.11 (1.08-1.14)	1.17 (1.01-1.35)	1.21 (0.97-1.51)	1.23 (1.05-1.42)	1.61 (0.90-2.86)	1.43 (0.88-2.30)
22									
23	WOMEN	N events/N [*]	Crude rate/100	Age (one year)	SBP(10	DBP (10	TC/HDL ratio	Diabetes	Current smoking
24			000 person-		mm/Hg)	mm/Hg)	(one unit)	(yes/no)	(yes/no)
24	Nova 7 and and		years (95% CI)						
25	New Zealana			HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
26	European women	757/10001	528 (402-567)	1 06 (1 05-1 07)	1.09(1.05-1.13)	1 13 (1 05-1 22)	1 1/ (1 00-1 21)	1 03 (1 50-7 35)	2 74 (2 20-2 27)
27	Indian women	106/7039	531 (439-643)	1.06 (1.03-1.07)	1 27 (1 16-1 39)	1 25 (1 03-1 50)	1.14(1.03-1.21) 1 21 (1 03-1 41)	2 29 (1 55-3 37)	2.74 (2.30-3.27) 2.60 (0.64-10.59)
28		100,7035	551 (455 645)	1.00 (1.05 1.00)	1.2, (1.10 1.55)	1.25 (1.05 1.50)	1.21 (1.05 1.41)	2.25 (1.55 5.57)	2.00 (0.04 10.00)
29	Norwegian cohort								
20	Norwegian women	259/8015	378 (335-427)	1.10 (1.09-1.12)	1.20 (1.12-1.28)	1.32 (1.18-1.47)	1.30 (1.19-1.43)	2.79 (1.52-5.11)	2.22 (1.73-2.84)
30	South Asian	26/967	341 (232-501)	1.14 (1.09-1.19)	1.06 (0.86-1.30)	1.07 (0.74-1.55)	1.04 (0.77-1.39)	2.74 (1.21-6.22)	†
31	women								

^{*}The numbers of events and people included in the analyses may differ due to missing risk factor data. Few were missing in the NZ cohort. [†]Not calculated due to no exposed cases.

DBP, diastolic blood pressure; HDL, high density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol.

Ethnic difference in CVD

South Asians of both genders in Norway and New Zealand had increased risk of CVD compared to the European majority populations (Table 3), with age-adjusted HRs ranging from 1.42-1.92. After adjustment for TC/HDL ratio and diabetes, the HRs for South Asians versus Europeans were reduced and no longer significant in women. Additional adjustments for SBP and smoking increased the hazard ratios again so that South Asians in both countries had significantly increased risk of CVD compared to Europeans. After adjustment for age, TC/HDL ratio, diabetes, SBP and smoking, the HRs for the excess risk in South Asians

full adjustment was seen in South Asian men in the Norwegian cohort where the HR was lowered by approximately 38% after adjusting for the four major risk factors. The smallest reduction in risk estimate after adjustment was among South Asian women in the New Zealand cohort where the risk estimate was only reduced by 7 % (from 1.42 - 1.39).

Table 3. Hazard ratios (95% CI) for first CVD event in South Asian groups compared to ethnic European groups in New Zealand and Norway.

		Men		Women	
	0	Indian vs. European NZ	South Asians vs. Norwegians	Indian NZ vs. European NZ	South Asians vs. Norwegians
N events/N Adjusted for		1791/73308	436/7387	863/56126	264/8558
	Age	1.75 (1.53-2.00)	1.92 (1.48-2.49)	1.42 (1.16-1.75)	1.87 (1.21-2.87)
	Age, TC/HDL ratio	1.77 (1.55-2.02)	1.66 (1.27-2.16)	1.41 (1.14-1.73)	1.52 (0.98-2.36)
	Age, TC/HDL ratio, diabetes	1.49 (1.30-1.71)	1.42 (1.08-1.87)	1.15 (0.92-1.42)	1.30 (0.82-2.04)
	Age, TC/HDL ratio, diabetes, SBP	1.57 (1.37-1.80)	1.53 (1.16-2.01)	1.19 (0.96-1.47)	1.31 (0.83-2.07)
	Age, TC/HDL ratio, diabetes, SBP, smoking	1.64 (1.43-1.88)	1.57 (1.19-2.07)	1.39 (1.11-1.73)	1.76 (1.09-2.82)

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

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

DISCUSSION

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

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

Strengths of the PREDICT cohort are the large sample size and the completeness of risk factors included in the risk-assessment. Only 0.01% were missing on any of the four major risk factors because they were part of the prediction algorithm and thereby compulsory to fill in to the PREDICT template. Furthermore, comprehensive national health registers were used to identify and exclude people with prior CVD and to determine cardiovascular outcomes. In the New Zealand cohort, some recruitment bias is likely since risk assessment was initially prioritized for high-risk patients. Indian patients are therefore over-represented in the cohort together with Maoris and Pacifics[19]. The representativeness of the source population is, however, improving as PREDICTs coverage increases. In this study, follow-up extended to 2012 when PREDICT included 50% of guideline-eligible patients in the practices where the PREDICT software is used[32]. We did not assume that the cohorts were representative of the general populations in the two countries, but that the ethnic groups within the two cohorts should be comparable. Adjusting for age was therefore particularly

important in the New Zealand cohort since South Asians were around seven years younger than Europeans. Results from the two cohorts showed approximately the same regarding ethnic differences, which is a strength concerning the external validity of these results. A limitation in the New Zealand data is short follow-up time restricting the statistical power. Another limitation is the lack of standardized BP measurements since recorded BP can easily be affected by a range of factors including the type of device used[33].

Strengths of CONOR data are the standardized measurements of risk factors, the linkage with disease outcomes from comprehensive national health registers and the standardized way of defining ethnicity using country of birth. A validation study examining the Oslo Health study, showed that participants with a non-western background had a lower participation rate than others[34]. This may reflect self-selection which can work both ways; healthy and resourceful people have the energy and motivation to participate or less healthy people who think their health could benefit from participating do so. Self-selection is unlikely to influence associations between risk factors and subsequent disease, but could influence the ethnic comparisons if the mechanisms were systematically different for the ethnic groups. The South Asian group in the Norwegian cohort was relatively small, which reduced the precision of the estimates and limited the statistical power. Another limitation in the CONOR data is missing information on some of the risk factors (see Tables A3-A6 in the Appendices for numbers of missing). However, the extent of missing was small. The risk factor with most missing in CONOR was diabetes (3% for the total cohort).

In both cohorts, the endpoints are based on register data, including both hospital and mortality data, which enables almost complete ascertainment of CVD events. In New Zealand, more than 95% of patients with an acute CVD event are managed by government-

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funded health services[19]. However, CVD events occurring among participants who travelled outside of New Zealand, those who emigrated after the index CVD risk assessment or among participants treated in private hospitals would not be captured in the national hospital and mortality registers [19]. We have no information about possible emigration for the New Zealand cohort, but for the Norwegian cohort we know that few people have emigrated (about 1% of the ethnic Norwegians and <3% of the South Asians who participated in the Oslo health studies had emigrated by the end of follow-up). A limitation for both cohorts is also the lack of medication data during follow-up. However, adjustment for baseline medication did not change the estimates (Tables A3-A4 in the Appendices), and Table 1 shows that South Asians used more antihypertensives and lipid lowering drugs at baseline than Europeans. Both countries have universal health care and South Asians should have the same access to cardiovascular medication as Europeans. It is therefore not likely that lack of treatment explains the differences in risk of CVD between the two ethnic groups. Our finding that the traditional major CVD risk factors contribute to the development of CVD in South Asians as in Europeans was an expected, yet important, finding since most knowledge about CVD prevention is based on studies in populations of European descent, and some have questioned whether these risk factors apply worldwide [11, 35]. This finding is in line with the large INTERHEART and INTERSTROKE case-control studies[11, 12], which reported that 90% of the population attributable risk for AMI and stroke worldwide was accounted for by respectively nine and ten (similar) risk factors, including those included in the present study. We are only aware of two other prospective studies reporting HRs for the prospective relationship between major CVD risk factors and subsequent CVD in South Asians [7, 36]. One of these studies included only men, [7] and the other showed estimates

for men and women combined and did not include blood lipids[36]. These studies generally

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 agree with our findings that traditional risk factors contribute to the development of CVD in South Asians as in Europeans[7, 36]. Also, consistent with previous reports[5, 6], we found that South Asians in both Norway and New Zealand have a higher risk of CVD compared to the European majority populations. By including all the measured risk factors (BP, TC/HDL ratio, diabetes and smoking) as adjustment variables in one statistical model, we could not explain the higher risk of CVD in South Asians. However, the increased risk was attenuated when we only included the risk factors more prevalent in South Asians than in Europeans (TC/HDL ratio and diabetes).

The excess risk of CVD among South Asians compared to Europeans in the Norwegian cohort was almost two-fold. This is comparable to what we reported previously when studying the total Norwegian population[5]. The South Asians in the New Zealand cohort had 42-75% higher risk of CVD compared to European New Zealanders which also agrees with previous New Zealand studies [6]. In both the Norwegian and New Zealand data, South Asians had higher baseline levels of dyslipidemia indicated by the TC/HDL ratio and higher diabetes prevalence compared to the European majority populations, which is in general agreement with previous knowledge from these countries[14-16]. Attenuation of the excess risk in South Asians versus Europeans was best achieved in the Cox model only including diabetes and TC/HDL ratio as covariates in addition to age. The same was found in both cohorts, clearly indicating that the unfavorable distribution of blood lipids and type 2 diabetes explains some of the higher risk of CVD in South Asians. South Asians generally have a high prevalence of metabolic risk factors related to insulin resistance, often clustered so that they match the concept of the metabolic syndrome[37-40]. A British cohort study that tested whether traditional risk factors could account for the high mortality of CHD among South Asian men compared to European men, reported that adjusting for insulin resistance,

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dyslipidemia and hyperglycemia in South Asians did not explain their higher risk[7]. However, they also adjusted for smoking and total cholesterol, which were both less prevalent/lower among South Asian men compared to European men.

It is unclear why the traditional risk factors do not completely explain the excess risk of CVD in South Asians. This could be related to incomplete adjustments; due to either imprecise measurement of risk factors or that other important risk factors were not included (e.g. waist measurement, length of time since diabetes diagnosis). A number of non-conventional risk factors are also thought to partially account for the high risk of CVD in South Asians, including dysfunctional HDL, C-Reactive Protein, thrombogenic risk factors, telomere length, high homocysteine levels and low birth weight[41, 42]. Socioeconomic factors could probably also explain some of the differences in risk between the ethnic groups, but we did not have such variables. Another possibility is that risk factors work cumulatively over time in the development of atherosclerosis, and some risk factors may also work at specific and crucial time points during the life course. Measurements taken on single occasions may also lead to an underestimation of the strength between the usual levels of the risk factors and later disease, known as the regression dilution bias [43]. Consequently, it is unlikely that the ethnic differences would disappear completely by adjusting for selected risk factors measured once in midlife.

Although South Asians seem to have an underlying susceptibility for metabolic diseases, traditional and modifiable risk factors are important for preventing disease. Our analyses indicate that it is important to focus on the prevention of type 2 diabetes and dyslipidaemia when aiming to reduce the burden of CVD among South Asians. The additional effect of abdominal obesity for the risk of CVD among South Asians in Norway and New Zealand has, BMJ Open: first published as 10.1136/bmjopen-2017-016819 on 6 December 2017. Downloaded from http://bmjopen.bmj.com/ on June 12, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES)

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however, not yet been studied although we know that the prevalence is high in this ethnic group[38, 44]. In both Norway[45, 46] and New Zealand,[47] intervention studies targeting immigrants from South Asia have been carried out with some promising results. A UK-study that prospectively examined the influence from four health behaviors on the risk of CVD in South Asian immigrants and UK Europeans found an important potential for disease prevention among South Asians if they adhered to healthy behaviors[8].

CONCLUSION

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

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VIEW Ethnicity Protocol

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

Table 1

Level 2 ethnic codes

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

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PREDICT 2015 baseline data – Unique ethnicity codes

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

Source	Variable name	Eth	nici	ty Co	odes									
	nt ethnic drown 1	10	11	12	2	1 :	30	31	32	33	34	35	30	37
	pt_ethnic_group_1	40	41 3 44	42 14 4	. 4. 441	54 14	441:	51 24	52 4413	55 444	54 14	44 444	15	+∠ NA
		10	11	12	2	1 :	30	31	32	33	34	35	30	37
PREDICT 2015	pt_ethnic_group_2	40	41	42	43	3 4	44	51	52	53	54	99	44	1
		443 44411 44412 44414 NA												
		10	11	12	2	1 :	30	31	32	33	34	35	30	5 37
	pt_etnnic_group_3	40	41	42	4. 1 /	י ל אוא	44	51	52	53	54	99	44	1
		10	11	444	21	30	31	32	33	34	35	36	37	40
	nhi_ethnicg1	41	42	43	44	51	52	53	54	61	94	95	97	99
Miniatory of	nhi_ethnicg2	10	11	12	21	30	31	32	33	34	35	36	37	40
Winistry of		41	42	43	44	51	52	53	54	61	94	95	97	99
		NA												
	nhi_ethnicg3	10	11	12	21	30	31	32	33	34	35	36	37	40
		41	42	43	44	51	52	53	61	97	99	ΝA		
NB: There are no	NAs in "nhi_ethnicg1"													

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

Procedure for Ethnicity Allocation

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

1) Is this person Maori? If yes, write "NZMaori", otherwise next question.

2) Is this person Pacific? If yes, write "Pacific", otherwise next question.

3) Is this person Indian? If yes, write "Indian", otherwise next question.

4) Is this person Chinese? If yes, write "Chinese", otherwise next question.

5) Is this person Asian? If yes, write "Asian", otherwise next question.

6) Is this person MELAA? If yes, write "MELAA", otherwise next question.

7) Is this person Other? If yes, write "Other", otherwise next question.

8) Is this person European? If yes, write "European", otherwise next question.

9) Is the ethnicity unknown, not answered, not identifiable? If yes, write "No_not_stated".

NB: MELAA = Middle Eastern, Latin American, African

VIEW REVISED Procedure for Ethnicity Allocation

1) Is this person Maori? If yes, write "NZMaori", otherwise next question.

2) Is this person Pacific? If yes, write "Pacific", otherwise next question.

3) Is this person Indian? If yes, write "Indian", otherwise next question.

4) Is this person Chinese? If yes, write "Chinese", otherwise next question.

5) Is this person Asian? If yes, write "Asian", otherwise next question.

6) Is this person European? If yes, write "European", otherwise next question.

7) Is this person MELAA? If yes, write "MELAA", otherwise next question.

8) Is this person Other? If yes, write "Other", otherwise next question.

9) Is the ethnicity unknown, not answered, not identifiable? If yes, write "No_not_stated".



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Multiple Ethnicities

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

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

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

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

The use of "OTHER" Ethnicity

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

Original "ag_eth" Classification

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

Problems with above coding convention:

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

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

Frequency

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

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

Proportion

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

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NEW "view_ag_eth" Classification

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

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

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

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

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

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

Frequency

Asian	Chinese	European	Indian	MELAA	No_not_stated	NZMaori
18745	26563	276433	39205	6797	654	62181
Other	Pacific	<na></na>				
2262	59305	0				
Proport	ion					
Asian	Chinese	European	Indian	MELAA	No_not_stated	NZMaori
0.038	0.054	0.562	0.080	0.014	0.001	0.126
Other	Pacific	<na></na>				
0.005	0.121	0.000				

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Appendix A

Prioritisation Output for Ethnicity

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

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

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

Limitations are that prioritised output:

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

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

Appendix

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

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

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

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

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

MEN	N events/N≠	SBP (10 mm/Hg)	SBP (10 mm/Hg) a for BP medication	adjusted T((c	C/HDL ratio one unit)	for lipid lowering medicati
<i>New Zealand cohort</i> European men Indian men	1518/63316	HR (95%CI) 1.15 (1.12-1.18) 1.05 (0.98-1.13)	HR (95%Cl) 1.14 (1.11-1.17) 1.03 (0.96-1.11)	H 1. 1	R (95%Cl) .20 (1.16-1.23) .08 (0.98-1.19)	HR (95%Cl) 1.20 (1.16-1.24) 1.10 (1.00-1.20)
Norwegian cohort	2/3/3337	1.05 (0.98-1.15)	1.03 (0.90-1.11)	1.	.08 (0.98-1.19)	1.10 (1.00-1.20)
Norwegian men South Asian men	379/6385 79/1239	1.15 (1.08-1.22) 1.17 (1.01-1.35)	1.13 (1.06-1.20) 1.14 (0.98-1.32)	1. 1.	.22 (1.15-1.30) .23 (1.05-1.42)	1.23 (1.16-1.31) 1.21 (1.04-1.42)
	Ċ	CDD/40		diverse de Tra		
WOIMEN	N events/N [≠]	SBP(10 mm/Hg)	for BP medication	adjusted 10 0 (a	C/HDL ratio one unit)	for lipid lowering medicati
New Zealand cohort				н	R (95%CI)	
uropean women	757/49094	1.09 (1.05-1.13)	1.07 (1.03-1.12)	1.	.14 (1.09-1.21)	1.15 (1.09-1.21)
ndian women	106/7039	1.27 (1.16-1.39)	1.23 (1.12-1.36)	1.	.21 (1.03-1.41)	1.22 (1.04-1.42)
Vorwegian cohort	250/0015	1 20 (1 12 1 20)	1 10 (1 11 1 1 26)	4	20 (1 10 1 42)	1 22 (1 21 1 46)
vorwegian women	223/2012	1.20 (1.12-1.28)	1.10 (1.11-1.20)	1.	.50 (1.19-1.43) 04 (0 77 1 20)	1.35 (1.21-1.40) 1.01 (0.75-1.27)
outh Asian women [#] The numbers of the NZ cohort. SE	26/967 events and peop P, systolic blooc	l pressure; TC, total c	halyses may differ due cholesterol; HDL, high	e to missing ris n density lipopi	sk factor data. Fe rotein.	w were missing in
South Asian women *The numbers of the NZ cohort. SE Table A4. Haza European grou baseline.	26/967 events and peop P, systolic blood ard ratios (95 ups in New Ze	% CI) for first CVI	halyses may differ due cholesterol; HDL, high D event in South A ay – with and with	e to missing ris n density lipopi Asian group: hout adjustr	sk factor data. Fe rotein. s compared to ment for medi	w were missing in ethnic ication at
iouth Asian women [≠] The numbers of the NZ cohort. SE Table A4. Haza European grou baseline.	26/967 events and peop P, systolic blooc ard ratios (95 ups in New Ze	% CI) for first CVI	halyses may differ due cholesterol; HDL, high D event in South A ay – with and with Men	e to missing ris n density lipopi Asian group: hout adjustr	sk factor data. Fe rotein. s compared to ment for medi Women	w were missing in 9 ethnic ication at
South Asian women *The numbers of the NZ cohort. SE Table A4. Haza European grou baseline.	26/967 events and peop P, systolic blood ard ratios (95 ups in New Ze	% CI) for first CVI ealand and Norwa	halyses may differ due cholesterol; HDL, high D event in South A ay – with and with Men Indian vs. European NZ	e to missing ris n density lipopi Asian groups hout adjustr South Asians v Norwegians	sk factor data. Fer rotein. s compared to ment for medi <u>Women</u> vs. Indian NZ v European N	w were missing in ethnic ication at s. South Asians vs. IZ Norwegians
South Asian women *The numbers of the NZ cohort. SE Table A4. Haza European grou baseline. N events/N	<u>26/967</u> events and peop P, systolic blood ard ratios (95 ups in New Ze	% CI) for first CVI ealand and Norwa	Aalyses may differ due cholesterol; HDL, high D event in South A ay – with and with Men Indian vs. European NZ 1791/73308	e to missing ris n density lipopi Asian groups hout adjustr Norwegians 436/7387	sk factor data. Fer rotein. s compared to ment for medi <u>Women</u> vs. Indian NZ v European N 863/561	w were missing in ethnic ication at s. South Asians vs. IZ Norwegians 26 264/8558
South Asian women *The numbers of the NZ cohort. SE Table A4. Haza European grou baseline. N events/N Adjusted for	<u>26/967</u> events and peop P, systolic blood ard ratios (95 ups in New Ze	% CI) for first CVI ealand and Norwa	Aalyses may differ due cholesterol; HDL, high D event in South A ay – with and with Men Indian vs. European NZ 1791/73308	e to missing ris n density lipopi Asian groups hout adjustr Norwegians 436/7387	sk factor data. Fer rotein. s compared to ment for medi <u>Women</u> vs. Indian NZ v European N 863/561	w were missing in ethnic ication at s. South Asians vs. IZ Norwegians 26 264/8558
South Asian women *The numbers of the NZ cohort. SE Table A4. Haza European grou baseline. N events/N Adjusted for Age, TC	<u>26/967</u> events and peop P, systolic blood ard ratios (95 ups in New Ze	etes, SBP, smoking	Analyses may differ due cholesterol; HDL, high D event in South A ay – with and with Men Indian vs. European NZ 1791/73308 1.64 (1.43-1.88)	e to missing ris n density lipopi Asian groups hout adjustr Norwegians 436/7387 1.57 (1.19-2.0	sk factor data. Fer rotein. s compared to ment for medi <u>Women</u> vs. Indian NZ v European N 863/561)7) 1.39 (1.11-:	w were missing in ethnic ication at s. South Asians vs. IZ Norwegians 26 264/8558 1.73) 1.76 (1.09-2.82)

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

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

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	Norwegian						ି Sonuth Asian ଟି ପ	
							ecen Ei	
	No. of persons	No. of CVD events	Crude rate/100 000 person-years (95% CI)	HR (95% CI)	No. of persons	No. of CVD events	ဖို့ဖြင့်ရှိ ဖြေဖျှင့် ဖြေဖျှင့် son-years (95% Cl)	HR (95% CI)
Total	6385	379	703 (636-778)		1239	79	6 6 6 6 6 6 6 6 6 6	
Diabetes						1	d nei 7.	
No	6167	339	649 (583-721)	1.00	1088	59		1.00
/es	101	28	3936 (2718-5701)	3.15 (2.14-4.65)	103	16	4 3 1 3 6 (1327-3536)	1.61 (0.90-2.86
Aissing	117	12	539 (298-973)		48	4	a 🚆 🛱 0 (416-2956)	
BP							d d deu	
:140	4701	198	493 (429-566)	1.00	1068	56	6 6 6 6 7 6 7 6 7 6 7 7 6 7 7 7 7 7 7 7 7 7 7	1.00
.40-159	1373	130	1150 (969-1366)	1.39 (1.10-1.74)	150	19	3 963 1 (1072-2636)	1.44 (0.83-2.49
160	296	51	2228 (1693-2932)	1.76 (1.28-2.42)	21	4	2.98 5 (1075-7634)	1.51 (0.53-4.28
Aissing	15	0			0	0		
C/HDL ratio								
5	4284	207	568 (495-650)	1.00	538	21	a 4 🙀 (325-765)	1.00
: 5	2090	170	980 (843-1139)	1.64 (1.34-2.00)	698	58	1105 (854-1430)	2.14 (1.30-3.52
Missing	11	2	2328 (582-9307)		3	0		
TC							an <u>ä</u>	
< 5 mmol/L	1930	68	410 (324-520)	1.00	407	19	6 60 (389-955)	1.00
: 5 mmol/L	4444	309	830 (742-927)	1.17 (0.90-1.53)	830	60	945 (734-1217)	1.49 (0.89-2.49
Aissing	11	2	2328 (582-9307)		2	0	ilar	
IDL							. te	
: 1.00 mmol/L	1032	78	915 (733-1142)	1.00	525	34	856 (611-1197)	1.00
:1.00 mmol/L	5343	299	660 (589-739)	0.61 (0.47-0.78)	711	45	82 82 (613-1099)	0.99 (0.63-1.55
Missing	10	2	2608 (652-10427)		3	0	20	
Current daily smokers							es.	
No	4706	231	578 (508-657)	1.00	905	52	74 (571-983)	1.00
′es	1660	146	1062 (903-1248)	1.86 (1.51-2.29)	302	25	128 (735-1610)	1.43 (0.88-2.30
Vissing	19	2	1236 (309-4941)		32	2	83 2 (208-3323)	

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able A6. Crude rates	and age-adjuste	ed HR of CVD	by risk factors, Norw	vegian and South	n Asian women	from the N	aht. includin frwegian cohort.	
	Norwegian				South Asian		or c	
	No. of persons	No. of CVD events	Crude rate/100 000 person-years (95% CI)	HR (95% CI)	No. of persons	No. of CVE events	Se fragerude rate/100 000 reigingerson-years (95% CI)	HR (95% CI)
Total	8015	259	378 (335-427)		967	26	S 41 (232-501)	
Diabetes							to 7.	
No	7657	237	361 (318-410)	1.00	816	17	g v \$62 (163-422)	1.00
Yes	105	11	1305 (723-2356)	2.79 (1.52-5.11)	100	9	a b 3212 (630-2329)	2.74 (1.21-6.2
Missing	253	11	539 (298-973)		51	0	nde	
SBP								
<140	6823	151	257 (219-302)	1.00	876	18		1.00
140-159	920	76	999 (798-1251)	1.82 (1.37-2.43)	67	4		1.45 (0.48-4.34
>160	266	31	1450 (1020-2062)	2.11 (1.42-3.15)	23	4	a . 3 78 (892-6335)	2.42 (0.76-7.7
Missing	6	1	2128 (300-15106)		1	0		
TC/HDL ratio							tra <mark>nj</mark> o	
<5	7225	203	328 (286-376)	1.00	749	17	87 (178-462)	1.00
≥5	781	54	833 (638-1088)	1.79 (1.33-2.42)	215	9	2 37 (279-1032)	1.46 (0.65-3.3)
Missing	9	2	3122 (781-12483)			0	an ^B .	
тс								
< 5 mmol/L	3004	44	169 (125-227)	1.00	524	8	E . 2 93 (97-386)	1.00
≥ 5 mmol/L	5002	213	503 (440-576)	1.40 (1.00-1.97)	440	18	a 521 (328-826)	1.54 (0.65-3.6
Missing	9	2	3122 (781-12483)		3	0	lun	
HDL							e 1:	
< 1.2 mmol/L	1057	52	587 (447-770)	1.00	465	12	329 (187-578)	1.00
≥1.2 mmol/L	6949	205	344 (300-395)	0.55 (0.40-0.74)	499	14	8 54 (210-598)	0.77 (0.36-1.6
Missing	9	2	3122 (781-12483)		3	0	at	
Current daily smokers							A g	
No	5461	134	285 (241-338)	1.00	883	24	9 44 (231-514)	1.00
Yes	2510	119	564 (471-675)	2.22 (1.73-2.84)	13	0	ce	
Missing	ЛЛ	6	1759 (790-3916)		71	2	3 65 (91-1/61)	

ease; HDL, high density lipoprotein; HR, hazard ratio: TC, total cholesterol; SBP, systolic blood program For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtme

		European					di Inglian	
							6 Dec	
	No. of persons	No. of CVD events	Crude rate/100 000 person-years (95% CI)	HR (95% CI)	No. of persons	No. of CV events	Do grade rate/100 000 grade son-years (95% CI)	HR (95% CI)
Total	63 319	1 518	815 (775-857)		9 997	273	e (828-1050)	
Type 2 diabetes							io1;	
No	57 760	1 2 4 1	728 (689-770)	1.00	7 641	158	d b 7 c c 1 2 (610-833)	1.00
Yes	5 559	277	1739 (1546-1957)	1.92 (1.68-2.19)	2 356	115	a J 2 (1351-1947)	1.72 (1.34-2.20)
Missing	0				0		xt ph	
SBP							oac	
<140	42 666	776	632 (589-678)	1.00	7 888	188	a S (698-929)	1.00
140-159	16 417	514	1030 (945-1123)	1.35 (1.20-1.51)	1 723	68	a → a → → (1128-1814)	1.37 (1.03-1.81)
>160	4 236	228	1675 (1471-1908)	2.03 (1.75-2.36)	386	17	<u>3</u>. 🛱 2 (909-2352)	1.22 (0.74-2.02)
Missing	0				0		nir S)	
TC/HDL ratio								
<5	45 177	994	756 (711-805)	1.00	6 379	178	A 92 (799-1072)	1.00
≥5	18 139	524	955 (876-1040)	1.58 (1.42-1.76)	3 617	95	a 945 (774-1157)	1.28 (1.00-1.65)
Missing*	3	0			1	0	nir per	
тс							9, <mark>5</mark>	
< 5 mmol/L	20 226	395	879 (797-970)	1.00	4 450	103	a 84 (693-1020)	1.00
≥ 5 mmol/L	36 071	684	756 (702-815)	1.01 (0.89-1.14)	5 130	137	o 974 (824-1152)	1.36 (1.05-1.76)
Missing*	7 022	439	861 (785-946)		417	33	1 11 4 (792-1567)	
HDL							lar ,	
< 1.00 mmol/L	2 325	55	986 (757-1284)	1.00	561	15	ହି 13ହୁଁ 7 (800-2202)	1.00
≥1.00 mmol/L	10 920	323	891 (799-993)	0.87 (0.66-1.17)	1 231	39	3 1140 (833-1561)	0.62 (0.33-1.14)
Missing*	50 074	1 140	789 (744-836)		8 205	219	88 (776-1011)	
Current daily smokers							gie 203	
No	55 587	1 197	733 (692-776)	1.00	9 105	242	919 (805-1035)	1.00
Yes	7 731	321	1396 (1252-1558)	2.29 (2.02-2.59)	892	31	1123 (790-1597)	1.45 (0.99-2.11)
Missing	1	0			0		l ge	

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

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

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able A8. Crude rates a	nd age-adjusted F	IR of CVD by r	isk factors, European	and Indian New Z	ealand women f	nt 01 in 68 romEtheoNe	ew Zealand cohort.	
	European				India	an n		
	No. of persons	No. of CVD events	Crude rate/100 000 person-years (95% CI)	HR	No. of persons	6 Decemb o Ens y forguses	Crude rate/100 000 person-years (95% CI)	HR
Total	49 094	757	528 (492-567)		7 039		531 (439-643)	
Type 2 diabetes						1017 1ted		
No	44 880	635	485 (448-524)	1.00	5 010	58 <u>1</u> 0	358 (271-472)	1.00
Yes	4 214	122	994 (832-1187)	1.93 (1.59-2.35)	2 029	56) ହେଁଛି	936 (720-1216)	2.29 (1.55-3.37
Missing	0				0	rt a		
SBP						nd		
<140	32 178	395	436 (395-481)	1.00	5 370	5 and the second	371 (285-482)	1.00
140-159	13 019	258	646 (572-730)	1.22 (1.04-1.44)	1 281	3an an a	919 (656-1286)	2.11 (1.37-3.26
>160	3 896	104	813 (671-985)	1.42 (1.14-1.77)	388		1388 (851-2266)	2.99 (1.70-5.27
Missing	1	0			0	ing .		
TC/HDL ratio						, <u>></u>		
<5	42 800	626	507 (469-549)	1.00	5 895	89 3	527 (428-648)	1.00
≥5	6 289	131	658 (555-781)	1.42 (1.17-1.71)	1 143		559 (347-898)	1.11 (0.66-1.86
Missing*	5	0			1			
тс						ຸ ຊ <u>ສ</u>		
< 5 mmol/L	10 940	127	515 (433-613)	1.00	3 277	5% 8	639 (493-828)	1.00
≥ 5 mmol/L	32 974	415	516 (469-569)	0.96 (0.79-1.17)	3 515	333	398 (289-550)	0.62 (0.41-0.94
Missing*	5 180	215	561 (491-641)		247	12gr on	689 (391-1212)	
HDL								
< 1.2 mmol/L	1 852	26	529 (360-776)	1.00	568	ne 9n	781 (406-1501)	1.00
≥1.2 mmol/L	7 985	149	578 (492-678)	0.97 (0.64-1.47)	866	1 <u>9</u> ,12	600 (355-1013)	0.75 (0.32-1.77
Missing*	39 257	582	517 (477-561)		5 605	20: 20:	504 (406-625)	
Current daily smokers						25 : \$S.		
No	43 994	595	466 (430-505)	1.00	6 973	104	526 (434-638)	1.00
Yes	5 100	162	1038 (890-1211)	2.74 (2.30-3.27)	66	2 b	1090 (272-4357)	2.60 (0.64-10.5
Missing	0				0	nc		

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

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

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

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

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies
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Section/Topic	ltem #	Recommendation	Reported on page #	
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1,2	
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5	
Objectives	3	State specific objectives, including any prespecified hypotheses	5	
Methods				
Study design	4	Present key elements of study design early in the paper	5	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-8	
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-8	
		(b) For matched studies, give matching criteria and number of exposed and unexposed		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-9	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-9	
Bias	9	Describe any efforts to address potential sources of bias	10	
Study size	10	Explain how the study size was arrived at	6-8,11	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10	
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9-10	
		(b) Describe any methods used to examine subgroups and interactions	9-10	
		(c) Explain how missing data were addressed	10	
		(d) If applicable, explain how loss to follow-up was addressed	10	
		(e) Describe any sensitivity analyses	10	
Results				

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	We did not have
			information about
			reasons for non-
			participation in
			CONOR, but
			participation rates
			are given on page 7
			and the possibility of
			self-selection bias is
			discussed on page
			18. This was not
			relevant for the
			PREDICT cohort since
			it was based on
			contact with the
			primary health care.
		(c) Consider use of a flow diagram	Different persons
			were involved in the
			exclusion of
			participants, so it
			was easier to
			describe this process
			in text.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential	11-13
		(b) Indicate number of participants with missing data for each variable of interest	Tables A2 AC in the
		(b) multate number of participants with missing data for each variable of interest	
		(c) Summarice follow up time (og everage and tetal amount)	appendices
Outcome data	15*	(c) summarise ronow-up time (eg, average and total amount)	12 (Table 1)
Outcome data	15**	Report numbers of outcome events or summary measures over time	15

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Main results	16	(<i>a</i>) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15-16
		(b) Report category boundaries when continuous variables were categorized	12 (in table legend) and 26-29
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Sensitivity analyses are reported on page 14, 16
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-22
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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