Scandinavian Cardiovascular Journal, 2012; 46: 316–323

informa
healthcare

ORIGINAL ARTICLE

Relative importance of risk factors for coronary heart disease – The Hordaland Homocysteine Study

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Abstract

Objectives. The aim was to rank coronary heart disease (CHD) risk factors according to their importance in predicting CHD morbidity and mortality using a scale-independent statistical approach. *Design.* We studied 15 515 community-dwelling adults in a population-based cohort established during 1992–93 in Western Norway. Participants were 40–42 and 65–67 years old at baseline and were followed through 2006. Endpoints were non-fatal/fatal acute myocardial infarction (AMI) and CHD death. Each factor was rank transformed and scaled to the range 0–5 before estimation of Cox models. Hazard ratios (HR) may thus be interpreted as HR per quintile increment for each factor, and the magnitude of the HR was used to rank the risk factors according to strength. *Results.* Total cholesterol and triglycerides were important risk factors for both CHD death and non-fatal/fatal AMI only in the middle-aged group. Risk factors were generally stronger in the middle-aged, except total homocysteine which was significantly associated with CHD death in the oldest group only. The only significant difference between men and women was found for single living which was an important risk factor for non-fatal/fatal AMI in middle-aged women but not in middle-aged men. *Conclusions.* We have demonstrated a simple method for direct and scale-independent comparison of the strength of both categorical and continuous risk factors. The importance of individual risk factors differed substantially between the two age groups.

Key words: *cardiovascular diseases, myocardial infarction, risk factors, cohort studies, incidence*

Introduction

During the last decades CHD mortality rates have declined in most industrialised countries (1,2). Several reasons for the decline have been proposed including decreased incidence, improved risk factors and better treatment. However, CHD is still the leading cause of death (3) and increased survival after CHD events have increased the prevalence of CHD and heart failure (4). Hospitalisation rates have not declined to the same extent as mortality rates (5,6), which indicates a continuous high burden of disease and makes primary prevention of CHD still an important challenge.

For both etiologic and prevention purposes, direct comparison of the importance, defined as the strength of an association, of various risk factors both within and between demographic groups would be advantageous. For instance, it is not clear to what extent the importance of individual risk factors differ between men and women or between different age strata.

Most comparisons of risk factors have been done by dichotomising both continuous and categorical factors in high and low risk groups with subsequent comparisons of relative risks and population attributable risks (PAR) (7–9). Dichotomisation of continuous risk factors such as blood pressure or cholesterol levels results in loss of information and the calculations of relative risks and PARs are sensitive to the chosen cut-off values. Several studies have used standardised regression coefficients and have thus been

Preliminary results from this study were presented as a poster at the EuroPrevent conference in Prague, Czech Republic in May 2010.
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(Received 20 March 2012; revised 3 August 2012; accepted 6 August 2012)

ISSN 1401-7431 print/ISSN 1651-2006 online © 2012 Informa Healthcare
DOI: 10.3109/14017431.2012.720024

limited to comparing continuous risk factor variables or have applied different types of explained-variance measures in regression models as measures of importance (10). However, such parameters describe degree of model fit and predictive accuracy rather than the relative importance of risk factors. Further, most studies on the effect of CHD risk factors use CHD mortality rather than incidence as the endpoint, and many studies have short follow-up time.

Our aim is to present a scale-independent ranking method that makes relative risk measures comparable for categorical and continuous risk factor variables and thus eliminates the need to categorise or dichotomise continuous variables. The method is demonstrated using data from the Hordaland Homocysteine Study (HHS), a large population-based cohort study (11). Data from HHS have previously been used to evaluate plasma total homocysteine and total cysteine as risk factors for death and cardiovascular disease (CVD) hospitalisations (12–14). The present study expands the previous reports by examining the relative importance of several risk factors in predicting both CHD death and fatal/non-fatal acute myocardial infarction (AMI) with 14 years of follow-up. Of particular interest was to examine whether the ranking of risk factors differed between age groups or gender.

Methods

Study population

The Hordaland Homocysteine Study (11) is a prospective population-based study including men and women living in Hordaland County, Western Norway, aged 40–67 years in 1992–93 with an overall participation rate of 72.7%. The study population in the present study are 17361 participants aged 40–42 years and 65–67 years at baseline. Information about pre-existing CVD (stroke, AMI, angina pectoris), diabetes and use of blood pressure medication was obtained from questionnaires. In addition, hospital discharge records from all hospitals in Western Norway were searched back in time in order to identify participants with previous hospitalisations due to AMI, stroke or diabetes. After excluding participants with CVD, diabetes or on blood pressure medication, 15515 participants where left for analysis.

Baseline measurements and risk factor definition

Details of baseline data collection have been previously reported (11,15). Briefly, height, weight and blood pressure were measured. Non-fasting blood samples were analysed for serum total cholesterol and triglycerides and plasma total homocysteine. Self-administered questionnaires included questions on marital status, education, medical history including CVD and diabetes, smoking, alcohol consumption, physical activity and history of CVD in first- degree relatives.

Alcohol consumption was not evaluated as a risk factor because a high proportion (30%) did not report number of alcohol units per week. In addition to male gender, four categorical variables (low education, living alone, physical activity, and CVD in first-degree relatives) and six continuous variables (pack-years of smoking, body mass index (BMI), serum triglycerides, serum total cholesterol, systolic blood pressure and plasma total homocysteine) were examined. For all risk factor variables a high score indicates a high risk.

Pack years of smoking for current and former smokers were calculated based on number of years smoked and average number of cigarettes smoked per day during the smoking period. Never smokers were assigned a zero value. Participants were defined as having CVD in first-degree relatives if at least one first-degree relative had a history of angina pectoris, AMI or stroke.

Follow-up and definition of endpoints

Participants were followed through 2006. The unique Norwegian personal identification number enabled linkage of baseline data from each participant to endpoints. Information on date and cause of death was obtained from the Causes of Death Registry, Statistics Norway. In addition hospital discharge records from all hospitals in Western Norway from 1992 to 2006 were searched for CVD hospitalisations. The underlying cause of death according to the International Classification of Disease (ICD9 from 1992 to 1995 and ICD10 from 1996 to 2006) and main and secondary diagnoses from hospitalisations were used to define two endpoints: CHD death (defined as death with underlying cause between 410 and 414 (ICD9) or I20 and I25 (ICD10)) and incident AMI (defined as a hospitalisation (fatal or non-fatal) with AMI (ICD9: 410, ICD10: I21, I22) as main or secondary diagnosis or death with AMI as the underlying cause). Only the first event during the follow-up period was used.

Statistical analysis

Differences in baseline characteristics between genders were tested using Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables.

In order to get both categorical and continuous risk factors on a common comparable scale, all

variables were rank transformed and scaled to units between 0 and 5 before further analysis. Values were sorted in ascending order and replaced by a rank from 1 to n where n is the number of observations with valid values for each variable. In the presence of ties the observations were given the same rank. The rank for tied observations was chosen as the average of the ranks that would have been given if there were no ties. For example if the ordered observations 10–20 were ties, these observations would get rank 15. After rank transformation the values were scaled to values between 0 and 5 according to the following formula:

$$\text{scaled risk factor} = (\text{rank}(\text{risk factor})/n) \cdot 5$$

A one-unit increase in the new rank transformed and scaled variable corresponds to one quintile increment in the original untransformed risk factor variable. For continuous variables, a one unit increase in the scaled factor always covers 20% of the distribution. The advantage is a scale indifferent to monotone transformations; regardless of units on the original scale, or whether a log-transformation was applied or not, the result of the rank transformation is always the same. This interpretation extends to ordered categorical variables, for example physical activity. As an illustration, assume physical activity is an underlying continuous variable, split into three categories. The scaled risk factor calculation for the categorised version yields the same result as for the continuous distribution, assuming each category is represented by its "median midpoint", that is, the value that splits the category in half (Figure 1, upper panel). In particular, for any dichotomised continuous variable, the span from the midpoint of the lower category to the upper will always be 50% on a percentile scale, thus corresponding to an increase of 5/2 on the quintile scale (Figure 1, lower panel).

This transformation is comparable to the relative index of inequality (RII) proposed by Pamuk (16) and later modified by Machenbach and Kunst (17), except for the choice of scaling factor.

After rank transformation and scaling, each factor was modelled separately with Cox Proportional hazards regression, specified as continuous variables. The estimated hazard ratio (HR) may thus be interpreted as HR per quintile increment both for continuous and categorical variables. The sizes of the HR's are directly comparable across models and factors and may be used as a measurement of the relative importance of the different factors. We made separate models for each age group with adjustment for gender. In addition we estimated models with mutual adjustments for all other risk factors and models stratified on both age group and gender. For continuous risk factors we also studied the association between the risk factors and the endpoints by modelling each transformed factor with three degrees of freedom smoothing spline fit in a Cox model (18). The association was visualised by plotting the predicted HR as a function of each risk factor scaled from 0 to 5 with confidence intervals.

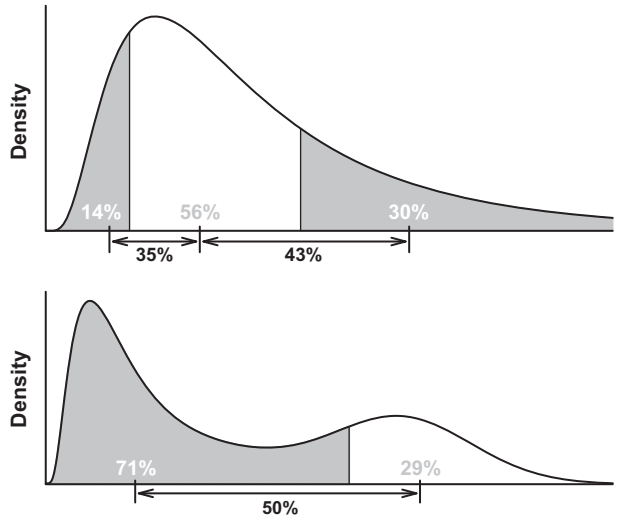

Figure 1. Upper panel: A continuous distribution categorised into three groups. Each category is represented by its "median midpoint", i.e. the value that splits the category in half. After rank transformation and scaling of the categorical variable a one unit increase in the risk factor corresponds to 20% (one quintile) of the original continuous distribution. Lower panel: A continuous distribution dichotomised at an arbitrary cutoff (here, the 71-percentile). The span from the median midpoint of the lower category to the upper covers 50% of the distribution, regardless of the shape of the distribution and the cutoff point on the original scale.

Statistical analyses were conducted using the statistical software SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) and R version 2.14.0 for Windows (R Foundation for Statistical Computing,Vienna, Austria).

Ethics

The Regional Committee for Medical and Health Research Ethics, the Data Inspectorate and the Norwegian Directorate of Health approved the study. Each participant signed an informed consent at baseline.

Results

Baseline characteristics, follow-up and endpoints

Baseline characteristics and summary of follow-up and endpoints for the 15515 participants are given in Table I, presented for older and younger men and

Table I. Baseline Characteristics in 1992–93, Follow-up and Endpoints in the Hordaland Homocysteine Study.

	Age 40–42		Age 65–67	
	Men	Women	Men	Women
Participants (n)	5907	6335	1365	1908
Age at examination, mean (sd)	40.8 (0.9)	40.8 (1.0)	66.0 (0.9)	66.0 (0.9)
Living alone, n (%)				
Single/divorced/separated/widow(er)	700 (11.9)	784 (12.4)	177 (13.0)	558 (29.3)
Married/Cohabitant	4209 (71.3)	4636 (73.2)	1046 (76.6)	1144 (60.0)***
Education, n (%)				
Primary and Secondary school	954 (16.2)	1551 (24.5)	439 (32.2)	890 (46.7)
High School	2108 (35.7)	2305 (36.4)	438 (32.1)	548 (28.7)
College/University	1806 (30.6)	1478 (23.3)***	302 (22.1)	173 (9.1)***
Smoking, n (%)				
Never smokers	1890 (32.0)	2476 (39.1)	320 (23.4)	1106 (58.0)
Former smokers	1595 (27.0)	1418 (22.4)	609 (44.6)	356 (18.7)
Current smokers	2418 (40.9	2434 (38.4)***	436 (31.9)	446 (23.4)***
Pack-years of smoking, median (20–80 pct)	7 (0–17.5)	2.73 (0–12.5)***	12.5 (0–28.2)	0 (0–11.25)
Physical activity, n (%)				
Sedentary/no physical activity	1029 (17.4)	1062 (16.8)	202 (14.8)	384 (20.1)
Light	3122 (52.9)	4531 (71.5)	915 (67.0)	1383 (72.5)
Moderate/High	1755 (29.7)	741 (11.7)***	247 (18.1)	140 (7.3)***
Body mass index (kg/m^2), median (20–80 pct)	24.9 (22.7–27.4)	23.3 (21.1–26.5)***	25.2 (22.9–27.7)	25.0 (22.2–28.4)
CVD in first-degree relatives, n (%)	2695 (45.6)	2998 (47.3)***	700 (51.3)	1157 (60.6)***
Physical measurements and biomarkers, median (20–80 pct)				
Total homocysteine, μmol/L	10.5 (8.8–12.8)	8.9 (7.3–11.2)***	11.9 (9.9–14.8)	10.7 (8.8–13.5)***
Total cholesterol, mmol/L	5.6 (4.8–6.6)	5.3 (4.6–6.1)***	6.2 (5.4–7.1)	7.0 (6.1–8.0)***
Triglycerides, mmol/L	1.6 (1.1–2.7)	1.0 (0.7–1.6)***	1.6 (1.0–2.5)	1.4 (1.0–2.2)***
Systolic blood pressure, mmHg	132.0 (122.0–143.5)	121.5 (112.0–134.0)***	145.0 (129.5–162.5)	144.0 (127.0–163.5)
Diastolic blood pressure, mmHg	79.5 (72.0–88.0)	75.0 (68.0–83.5)***	85.0 (76.0–95.5)	81.0 (72.5–92.0)***
Person-years of follow-up	83023	89385	16646	24796
Median follow-up time, years	14.2	14.2	14.0	13.9
All-cause deaths, n (%)	167 (2.8)	111 (1.7)***	422 (30.9)	347 (18.2)***
CHD deaths, n (%)	32 (0.54)	4 (0.1)***	71 (5.2)	29 (1.5)***
AMI hospitalisation/AMI death, n (%)	194 (3.3)	34 (0.5)***	203 (14.9)	129 (6.8)***

CVD = cardiovascular disease; CHD = coronary heart disease; AMI = acute myocardial infarction.
*P < 0.05, **P < 0.01, ***P < 0.001.
All p-values are two-sided p-values for difference between men and women in the same age group. For categorical variables with more than two levels the p-values are from the overall chi-square test.

women separately. The distribution of risk factors differed significantly between men and women in the same age group.

Median follow-up time with respect to CHD death and hospitalisations was approximately 14 years during which 1047 of the participants died (136 from CHD). A total of 560 participants had at least one hospitalisation or death caused by AMI. As expected, men suffered more endpoints than women in the same age group.

Relative importance of risk factors

Results from gender-adjusted Cox- regression analyses for each risk factor and both endpoints are given in Figure 2. Spline plots for the association between the continuous risk factors and the two endpoints are given in Figure 3, stratified by age group and adjusted for gender. The HRs for the models in Figure 2 plus additional models with multiple adjustments for all other risk factors are given in supplementary materials (eTables I—II) which is only available in the online version of the journal. Please find this material with the following direct link to the article: http://informahealthcare.com/doi/abs/10.3109/14017431.2012.720024).

Cox-models and spline plots for incident AMI stratified on gender and age group are given in supplementary materials (eFigures 1–2) which is only available in the online version of the journal. Please find this material with the following direct link to the article: http://informahealthcare.com/doi/abs/10.3109/14017431.2012.720024).

Models with CHD death as endpoint were not stratified on gender because of very few events among the youngest women.

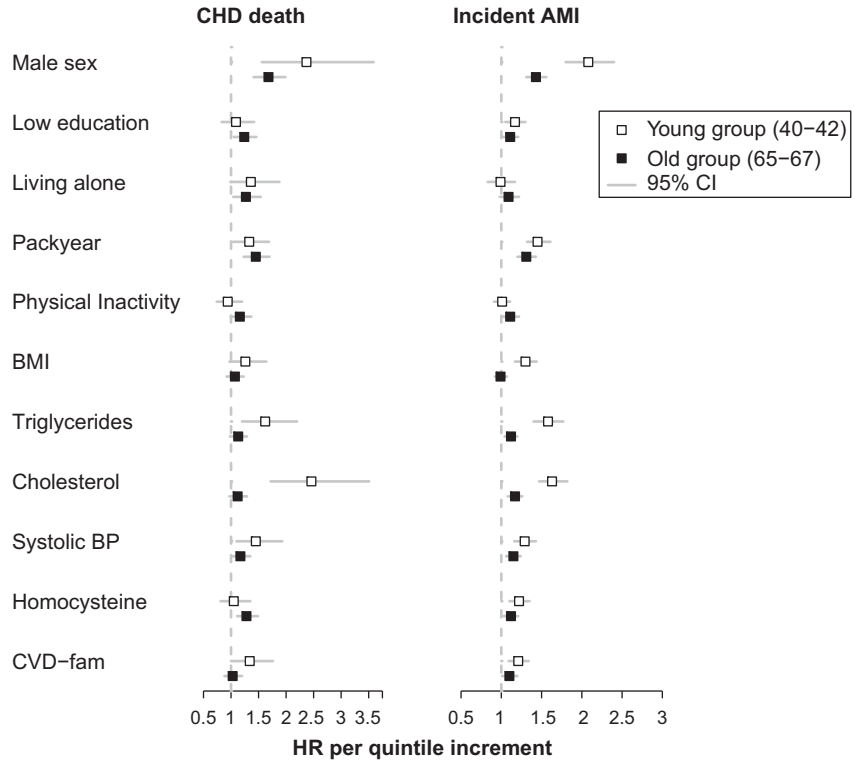

Figure 2. Hazard Ratios from Cox-models in two age strata for the 15515 participants in the Hordaland Homocysteine Study. Each risk factor is modelled separately adjusted for gender and with the endpoints CHD death and Incident AMI. CVD-fam = Cardiovascular disease in first-degree relatives.

CHD death. According to the relative sizes of HR's in Figure 2, the three most important risk factors for CHD death in the youngest group after adjustment for gender were total cholesterol, triglycerides, and systolic blood pressure. The associations for total cholesterol and triglycerides remained strong also after adjustment for other risk factors (eTable I). In the oldest group most associations between risk factors and CHD death were weak compared to the youngest group and total cholesterol and triglycerides were not associated with CHD death. The most important factors after adjustment for gender were pack years of smoking and total homocysteine.

BMI was also more important in the youngest group, but the change in HR per quintile increment was smaller, mainly caused by a U-shaped association (Figure 3). The minimum risk was at approximately 2.5 on the rank transformed scale which corresponds to a BMI of approximately 24 kg/m^2. In contrast total homocysteine was a significant risk factor for CHD death only in the oldest group, where the association between quintile increments of total homocysteine and CHD death was positive and approximately linear. The association remained significant after adjustment for other risk factors (Supplementary eTable I to be found online at http://informahealthcare.com/doi/abs/10.3109/14017431.2012.720024).

Incident AMI. After adjustment for gender, the three most important risk factors for the combined non-fatal/fatal AMI endpoint in the youngest group were total cholesterol, triglycerides and pack years of smoking. Total cholesterol and triglycerides were almost equally important and the associations remained strong also after adjustment for the other factors (Supplementary eTable II to be found online at http://informahealthcare.com/doi/abs/10.3109/14017431.2012.720024). In the oldest group pack years of smoking was the most important risk factor.

In accordance with the results for CHD death, large differences between the two age groups were observed for the importance of total cholesterol and triglycerides. However, for AMI the associations were also present but weak in the oldest group. BMI was also important only in the youngest group. The spline plot for BMI in the youngest group was J-shaped, with increased risk only after the second quintile.

Further stratification on gender revealed some differences between men and women in the youngest age group. The association between BMI and incident AMI in young men was strong and linear while young women had a U-shaped and thus weaker association (Supplementary eFigure 2 to be found online at http://informahealthcare.com/doi/abs/10.3109/14017431.2012.720024), however the interaction

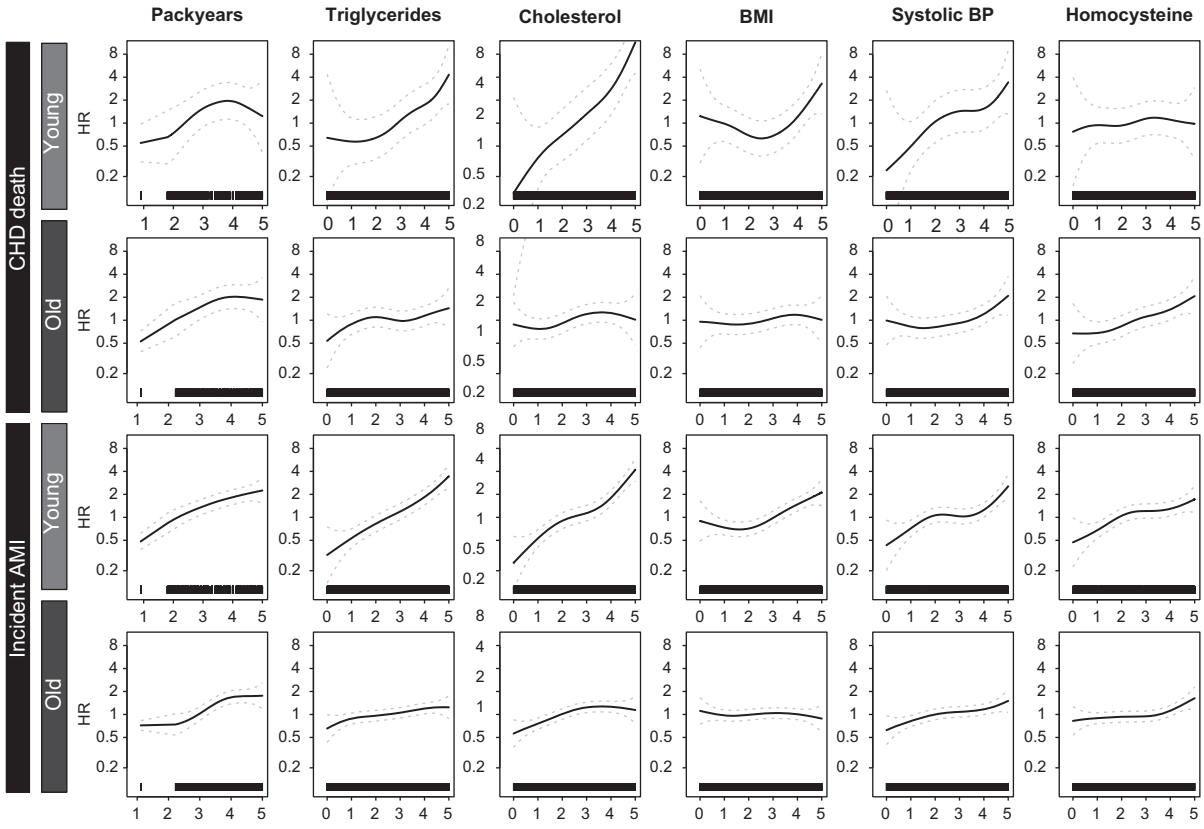

Figure 3. Gender-adjusted spline plots for each risk factor in two age strata and with the endpoints CHD death and Incident AMI for the 15515 participants in the Hordaland Homocysteine Study. Each risk factor is rank transformed and scaled from 0 to 5 before estimation.

between sex and BMI was not significant. For living alone and low education the effect was stronger in young women than in young men (Supplementary eFigure 1 to be found online at http://informahealthcare.com/doi/abs/10.3109/14017431.2012.720024). A test for interaction with sex revealed significant interaction for living alone ($p = 0.04$), but not for low education ($p = 0.08$).

Discussion

A fairly simple transformation method before estimation of HRs enabled direct comparisons of both categorical and continuous risk factors. Associations between risk factors and CHD endpoints were generally stronger among participants aged 40–42 years at baseline compared to those aged 65–67 years, with serum total cholesterol and triglycerides being the most important risk factors for both CHD death and incident AMI in the youngest group. No association with CHD death and only a weak association with incident AMI were found for total cholesterol and triglycerides in the oldest group. The same pattern was seen for BMI with a distinct U-shaped association with CHD death in the younger age group and no association in the older age group. Plasma total homocysteine was significantly related to CHD death in the oldest age group only. BMI was a strong risk factor for incident AMI in young men but not in young women and living alone and low education were important risk factors only in young women, although only living alone showed a significant interaction with sex. Thus, the importance of CHD risk factors differed between the two age groups and between men and women in the young age group.

Strength and limitations

To our knowledge this is the first study which directly compares the relative importance of both categorical and continuous CHD risk factors in a prospective setting. The study has a long follow-up time and includes both morbidity and mortality endpoints. The cohort included both middle-age and older participants enabling comparisons of the importance of risk factors across gender and age groups.

Our goal was to present a scale-independent relative risk measure. The rank transformation and scaling to a common scale for both continuous and categorical risk factors offers the opportunity to compare their importance without categorising

continuous risk factors and thus losing information. The risk estimates used in the present study is, however, dependent on the range for the individual risk factors in the study population. The HRs are thus not directly transferable to other populations with other risk factor ranges, although the relative ranking of each risk factors can still be compared between populations. We do not address the issue of relative versus absolute risk, nor the calculation of attributable risk.

The models in this study do not take into account clustering and possible interaction between risk factors, but the aim was to compare the strength of association for different risk factors rather than establishing risk models for best possible prediction of outcome.

One possible weakness with the study is that the diagnosis of non-fatal AMI was based only on discharge diagnoses from the hospitals' administrative systems without validation against the patient's medical record. The validity of administrative diagnoses for CVD has not been investigated in Norway, however the AMI diagnosis in the Danish National Patient Registry has been validated (19,20). In both studies on myocardial infarction the events with AMI as main diagnosis in the registry had a positive predictive value above 90% and a sensitivity of almost 80%. We may assume a similar validity in corresponding Norwegian data. There is no reason to suspect that the misclassification rate of about 20% for AMI is associated with any of the risk factors in our study.

Each risk factor was measured only at baseline and the possibility of regression-dilution bias during follow-up is present (21). In addition we did not have any information about use of antihypertensive drugs or lipid-lowering drugs during the follow-up period, but we did exclude all participants who had established CVD or reported using blood pressure medication at baseline in order to minimise this problem.

Comparison with previous work

In the oldest age group there was no significant association of total cholesterol, triglycerides and BMI with CHD and only a weak association with triglycerides and total cholesterol for incident AMI. The lack of an association between total cholesterol and cardiovascular endpoints in the elderly is in line with previous findings (9,22). A study by Corti et al however, found a positive association between total cholesterol and CHD death in the elderly after adjustment for different measures of frailty and poor health (23). The U- shaped associations between BMI and CHD in the youngest age group is also consistent with published results (24,25), although some studies have found associations which are J-shaped like the association for incident AMI in the present study (26,27). For non-fasting triglycerides there are conflicting results in the literature, but some studies have found stronger associations with AMI in younger age groups (28) in agreement with the present study.

Conclusion

Direct comparisons between several CVD risk factors revealed that non-fasting triglycerides were a very strong risk factor for both CHD death and incident AMI in middle-aged men and women. The importance of non-fasting triglycerides was comparable to the importance of total cholesterol even after adjustment for other risk factors. Risk factor associations were generally stronger in the youngest age group, except for the association between total homocysteine and CHD death which was only significant in the oldest group. The fairly simple rank transformation and scaling method demonstrated in this study provides a simple and useful tool for comparison of the importance of both categorical and continuous risk factors. This approach is applicable to other chronic disease areas for which several potential risk factors are to be compared.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary material available online

Supplementary eFigures 1-2.
Supplementary eTables I-II.