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Coronary heart disease risk factors ranked by importance for the individual and community

A 21 year follow-up of 12 000 men and women from The Copenhagen City Heart Study

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Aims The importance of coronary heart disease risk factors may differ between individuals and community and by sex and age.

Methods and Results The Copenhagen City Heart Study followed for 21 years a random sample of 5599 men and 6478 women aged 30 to 79 years at baseline. The importance of risk factors in individuals and the community were evaluated as relative- and population-attributable risks. We traced 2180 coronary events. In Cox regression analysis with ten risk factors entered simultaneously, relative risks for coronary heart disease in men ranged from 1·69 to 1·20 with the highest risks for diabetes, hypertension, smoking, and physical inactivity. In women, relative risks ranged from 2·74 to 1·19 with the highest risks for diabetes, smoking, hypertension, and physical inactivity. Population-attributable risks in men ranged from 22% to 3% with the highest risks for smoking, hypertension, and no daily alcohol intake. In women, attributable risks ranged from 37% to 3% with the highest risks for smoking, hypertension, and hypercholesterolaemia. Several of these rankings differed by age.

Conclusions The importance of coronary heart disease risk factors may differ for individuals, the community, and by sex and age. Consequently, prevention strategies should be tailored accordingly.
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Key Words: Coronary disease, relative and population attributable risks.

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Introduction

Mortality from coronary heart disease has declined steadily in industrialized countries in the past 20 to 30 years, undoubtedly due to primary and secondary prevention and to improved treatment[1,2]. Whilst it is credible that these measures have played a role, other factors may also have been influential. Unfortunately coronary heart disease is still the leading cause of death, which means there must be no let up in our attempts to eliminate this disease. Knowledge of prevention is based on prospective population studies started in the late 1940s, and on intervention trials undertaken since the early 1970s. These scientific approaches led to delineation of major coronary heart disease risk factors, a term that first appeared in a Framingham publication in 1961[3].

Based on this scientific evidence the American Heart Association, the World Health Organisation, the European Society of Cardiology and other bodies have implemented knowledge of prevention to the individual, as well as to the population at large. These prevention strategies have been applied to both men and women, and to most age groups. However, it is not clear whether the relative importance of the various risk factors is the same in the individual, the community, both genders, or in all age strata.

We therefore asked two questions for men and women separately stratified as young (30–54 years), middle aged (55–64 years) and elderly (65–79 years) at baseline: (1) What is the ranking of ten major coronary heart disease

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risk factors by importance for the individual? (2) What is the ranking of the same risk factors by importance for the community? The importance of risk factors in individuals and in the community was evaluated as relative risks and population-attributable risks, respectively.

Methods

Study population

The Copenhagen City Heart Study is a prospective cardiovascular population study comprising a random sample of 19 329 white men and women aged 20 years or older drawn from the Copenhagen Population Register as of 1 January 1976[4]. The first examination was from 1976 to 1978. The participation rate was 74%, which means that 14 223 persons were examined. In the present analysis, we included persons who fulfilled the following baseline criteria: were 30 to 79 years of age at entry, had no history of coronary heart disease, and information was available on all ten coronary heart disease risk factors included. Of available participants, 738 were excluded because they were not aged 30 to 79 years old at the time of the examination, 293 were excluded because they had a history of coronary heart disease when examined, and 1115 were excluded due to incomplete information on all 10 risk factors examined. So in the present analysis we included 12 077 persons, 5599 men and 6478 women.

Risk factors

Established procedures and examinations for cardiovascular epidemiological surveys were employed[5]. A self-administered questionnaire including information about smoking and alcohol intake, leisure time physical activity, socioeconomic status, and presence of diabetes mellitus was completed. All questionnaires were checked during the examination by the staff in collaboration with the participant; when data from the questionnaire were examined, we found significant discriminative power. Concentrations of total cholesterol, triglycerides, and glucose were measured in non-fasting plasma using enzymatic methods[4]. Body mass index was weight in kilograms divided by the square of the height in metres. Blood pressure was measured in the sitting position, on the left upper arm, after 5 min rest by use of a London School of Hygiene Sphygmomanometer.

In this analysis ten baseline coronary heart disease risk factors were included. They were dichotomized in reference and risk parts according to international recommendations for primary prevention of coronary heart disease[6]. Risk parts were (1) current smoking, (2) hypertension (systolic blood pressure ≥ 140 mmHg and/or use of antihypertensive drugs), (3) diabetes mellitus (self-reported disease, use of insulin, use of oral hypoglycaemic drugs and/or non-fasting plasma glucose $\geq 11{\cdot}1$ mmol . l^{-1}), (4) hypercholesterolaemia (plasma cholesterol $\geq 6{\cdot}0$ mmol . l^{-1}) (as roughly 80% of the participants had cholesterol level above 5 mmol . l^{-1}, we chose 6 as our cut off point), (5) hypertriglyceridaemia (plasma triglycerides $\geq 2{\cdot}0$ mmol . l^{-1}), (6) obesity (body mass index ≥ 25 kg . m^{-2}), (7) no daily alcohol intake, (8) physical inactivity during leisure time (almost entirely sedentary or light physical activity less than 2 h per week), (9) low or middle income, and (10) lower school education (≤ 10 years).

End-points

All subjects were followed from the first examination in 1976 to 1978 until development of coronary heart disease, death, or until 31 December 1997. Coronary heart disease (codes 410 through 414 of the Eight International Classification of Diseases) was identified through The National Patient Register (hospitalizations), The National Register of Courses of Death and The Civil Registration System, as well as through follow-up examinations in 1981 to 1983 and 1991 to 1994. The completeness of case finding from our sample was more than 95% of cases[7].

Statistics

Incidence rates were based on numbers of first time coronary heart disease events divided by 10 000 person-years of observation within 21 years of follow-up. Associations between dichotomized risk factors and development of coronary heart disease were tested with Cox proportional hazards regression: the model included all ten risk factors and used age as the underlying time scale with delayed entry accordingly. This means that age is adjusted for in all analyses, and that the observed relative risk for a given risk factor is that remaining after variations in age as well as the nine other risk factors have been accounted for. Interactions between risk factors and sex and age on coronary heart disease risk were examined. Relative risk was calculated as hazard ratio, and population-attributable risk as [f (RR-1)]/[1+f (RR-1)], where f is the frequency of the risk factor in the population at baseline and RR is the relative risk for coronary heart disease[8]. We used the statistical software packages SAS and Stata. *P*-values $<0{\cdot}05$ on two-sided tests were considered statistically significant.

Results

End-points

During 21 years of follow-up from 1976 to 1997 of 12 077 white men and women representing the Copenhagen general population, we traced 1304 men

Table 1 Incidence of coronary heart disease (CHD) during a 21-year follow-up by gender and age

	All	Age (years)		
		30–54	55–64	65–79
Men				
No.	5599	2893	1728	978
No. of CHD (% CHD deaths)	1304 (25·4)	487 (17·0)	501 (27·9)	316 (34·2)
Incidence: No./10 000 person-year	154	96	210	322
Women				
No.	6478	3394	2102	982
No. of CHD (% CHD deaths)	876 (20·7)	265 (15·1)	346 (20·2)	265 (26·8)
Incidence: No./10 000 person-year	78	41	99	204
Men/Women				
Incidence men/incidence women	2·0	2·3	2·1	1.6

and 876 women, in all 2180 incident cases of coronary heart disease (Table 1). Sixty-one percent of the cases were myocardial infarctions, and 24% of the cases were fatal. The 2180 cases were diagnosed via Danish national databases covering all causes of hospitalizations and deaths, with almost 100% follow-up. In addition, we performed follow-up examinations in 1981–83 and 1991–94. When we used this approach previously, we were successful in documenting more than 95% of cases[7].

Coronary heart disease incidence in men was approximately twice that of women in the young (30–54 years) and middle aged (55–64 years), while this sex difference was less pronounced in the elderly (65–79 years) (Table 1).

Risk factors

For men, the most common risk factors were lower school education, low or middle income, smoking, obesity, no daily alcohol intake and hypertension. For women, the most frequent risk factors were lower school education, no daily alcohol intake, low or middle income, smoking and hypercholesterolaemia (Table 2).

Frequency of diabetes mellitus, hypertension, physical inactivity, low or middle income, and lower school education increased as a function of age in both genders (Fig. 1). Frequency of hypercholesterolaemia, obesity, and hypertriglyceridaemia increased as a function of age in women only. Finally, frequency of smoking decreased as a function of age while frequency of no daily alcohol intake was fairly constant in the three age strata.

Ranking by relative risk

Stratified on sex

All ten risk factors examined were dichotomized to obtain a single relative and population-attributable risk for each factor (Table 2). This allows simple comparison and thus ranking by importance of all ten risk factors. In Cox regression analysis with ten risk factors entered simultaneously, significant relative risks for coronary heart disease in men ranged from 1·69 to 1·20 with the highest risks for diabetes mellitus, hypertension, smoking, and physical inactivity (Table 2). In women, significant relative risks ranged from 2·74 to 1·19 with the highest risks for diabetes mellitus, smoking, hypertension, and physical inactivity.

Gender interacted with diabetes mellitus, smoking, no daily alcohol and hypertriglyceridaemia on coronary heart disease risk (P=0·007, P<0·001, P=0·05 and P=0·006, respectively). Diabetes mellitus, smoking, and hypertriglyceridaemia conferred higher relative risks in women than in men, whereas no daily alcohol intake just conferred higher relative risk in men, but not in women (Table 2).

When we used cholesterol ≥ 5 mmol . l^{-1} in the Cox regression models (instead of ≥ 6 mmol . l^{-1} as in Table 2), hypercholesterolaemia had a relative risk of 1·21 (95% CI: 1·03–1·43, P=0·02) and 1·25 (95% CI: 0·94–1·65, P=0·13) for men and women. This amounts to a 6th and 8th rank in men and women, respectively. Other risk factors had unchanged relative risks compared with those shown in Table 2.

Stratified on age

Most risk factors conferred a similar risk of coronary heart disease in the young, middle aged, and elderly (Fig. 1); however, hypercholesterolaemia, hypertriglyceridaemia and school education interacted with age on risk of coronary heart disease in men (P=0·003, P=0·011 and P=0·013, respectively) (Table 2). The interactions with hypercholesterolaemia and hypertriglyceridaemia were explained by the fact that these two factors just conferred higher risk in the younger age group. The interaction with school education was explained by a lower risk of coronary heart disease conferred by lower school education in elderly men, but not in young or middle aged men.

***Table 2** Ranking of risk factors by relative risk and population-attributable risk in men and women*

Ranking by relative risk (RR)	RR (95% Cl)	Frequency (%)	Ranking by population-attributable risk (PAR)	PAR
Men				
1. Diabetes mellitus	1·69 (1·35–2·12)¶	4	1. Smoking	22*
2. Hypertension	1·46 (1·30–1·64)	48	2. Hypertension	18*
3. Smoking	1·41 (1·24–1·60)¶	71	3. No daily alcohol intake	12*
4. Physical inactivity	1·28 (1·13–1·47)	20	4. Obesity	10†
5. No daily alcohol intake	1·24 (1·11–1·38)¶	56	5. Hypercholesterolaemia	9*
6. Hypercholesterolaemia	1·22 (1·09–1·36)‖	47	6. Physical inactivity	5*
7. Obesity	1·20 (1·07–1·36)	57	7. Diabetes mellitus	3*
8. Low or middle income	1·14 (0·98–1·32)	78	8. Low or middle income	(10)
9. Hypertriglyceridaemia	1·06 (0·95–1·19)‖¶	40	9. Hypertriglyceridaemia	(2)
10. School education ≤10 years	1·01 (0·85–1·19)‖	84	10. School education ≤10 years	(1)
Women				
1. Diabetes mellitus	2·74 (1·99–3·78)¶	2	1. Smoking	37*
2. Smoking	2·02 (1·75–2·33)¶	58	2. Hypertension	14*
3. Hypertension	1·42 (1·23–1·64)	40	3. Hypercholesterolaemia	12‡
4. Physical inactivity	1·36 (1·17–1·59)	19	4. Obesity	7§
5. Hypertriglyceridaemia	1·33 (1·14–1·55)¶	19	5. Physical inactivity	7*
6. Hypercholesterolaemia	1·23 (1·06–1·43)	57	6. Hypertriglyceridaemia	6*
7. Obesity	1·19 (1·04–1·37)	39	7. Diabetes mellitus	3*
8. School education ≤10 years	1·28 (0·97–1·68)	89	8. School education ≤10 years	(20)
9. Low or middle income	1·22 (1·00–1·50)	82	9. Low or middle income	(15)
10. No daily alcohol intake	0·99 (0·81–1·21)¶	88	10. No daily alcohol intake	(−1)

Ranked by magnitude of relative risks (with 95% confidence interval) or population-attributable risks, with significant associations followed by those not reaching significance. Relative risks and population-attributable risks were calculated using Cox regression models, including age (as underlying time scale) and the 10 dichotomized risk factor variables. Frequency (%) denotes the prevalence of each risk factor using the dichotomized criteria given in the Methods section. Based on relative risks at *P<0·001; †P<0·005; ‡P<0·01;§P<0·05; values in parenthesis indicate that the attributable risk was non-significant. ‖Interaction by age; ¶interaction by sex.

Ranking by population-attributable risk

Stratified on sex

Population-attributable risks in men based on significant relative risks ranged from 22% to 3%, with the highest risks for smoking, hypertension, no daily alcohol intake, and obesity (Table 2). In women, attributable risks ranged from 37% to 3% with the highest risks for smoking, hypertension, hypercholesterolaemia, and obesity.

The largest gender difference in population-attributable risk was for smoking with attributable risks of 22% and 37% in men and women, and for no daily alcohol intake with attributable risks of 12% in men and no contribution in women, respectively.

When we used cholesterol ≥5 mmol . l^{-1} in the Cox regression models (instead of ≥6 mmol . l^{-1} as in Table 2), population-attributable risks for hypercholesterolaemia were 15% and 18% for men and women (based on a non-significant relative risk for women). This amounts to a 3rd and 8th rank in men and women, respectively. Other risk factors had unchanged population-attributable risks compared with those shown in Table 2.

Stratified on age

Most risk factors conferred a similar population-attributable risk of coronary heart disease in the young, middle aged, and elderly (Fig. 1). However, the population-attributable risk of smoking decreased clearly as a function of age in both genders, whereas we found an increment in population-attributable risk for hypertension in age for both genders. It was a surprise to find the low population-attributable risk for elderly men with lower school education.

Discussion

In this observational study of the general population we diagnosed 2180 coronary events among 12 077 individuals followed for 21 years and found significant associations to well known coronary heart disease risk factors for both sexes and in most age groups. This supports general recommendations of risk factor modification in both sexes and for all adult age groups. However, we also observed remarkable and relatively important differences in the various risk factors between sexes and between age groups, most importantly between the individual and the community. This suggests that prevention strategies should be tailored to each individual person, strategies that may differ from advice given to the population at large.

For all age groups we found an incidence of coronary heart disease in men approximately twice that found in women, with a narrowing of this sex difference with

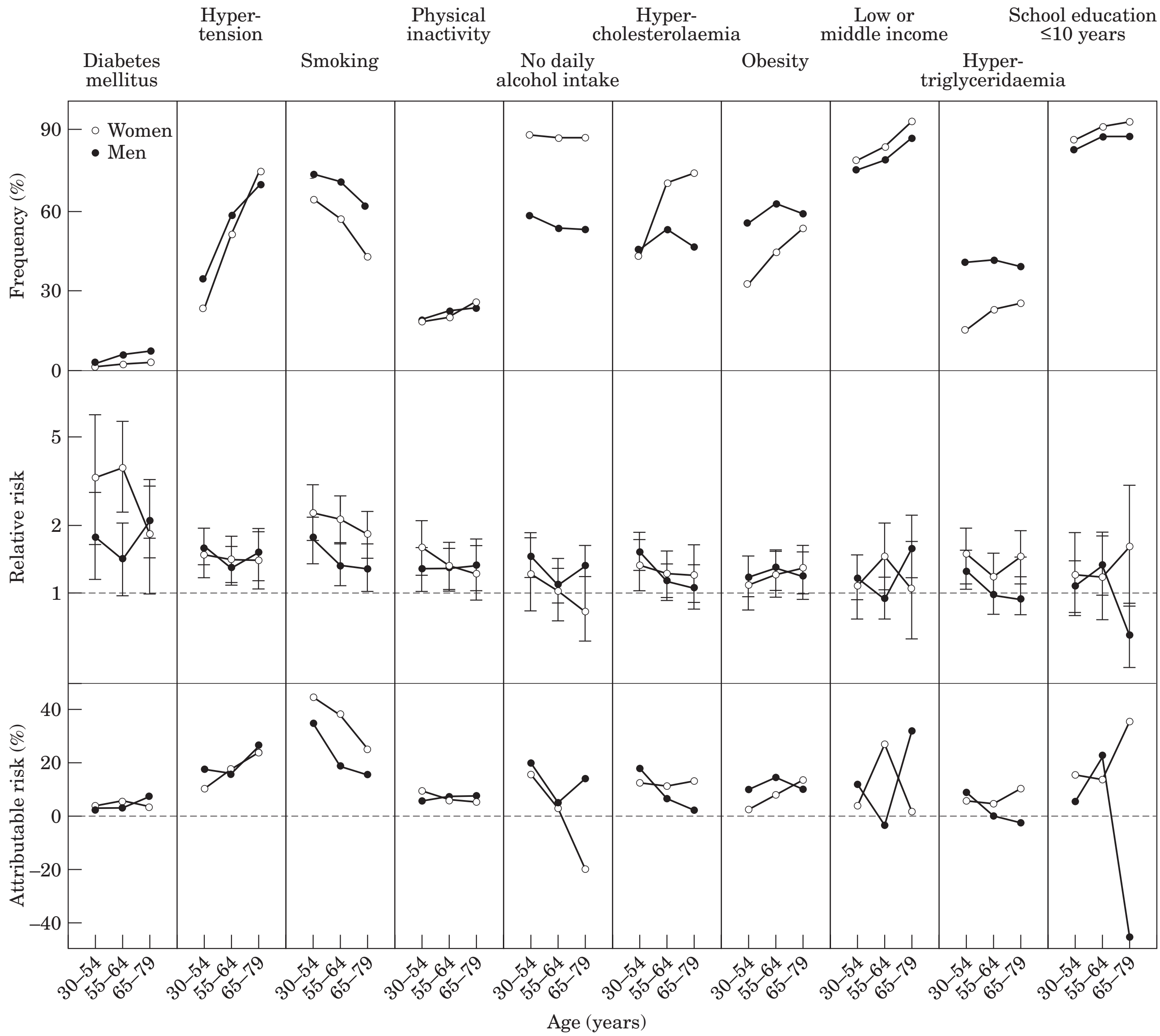

Figure 1 **Frequency, relative risk, and population-attributable risk of ten dichotomized coronary heart disease risk factors. Values are shown stratified for young (30–54 years), middle aged (55–64 years), and elderly (65–79 years) participants. Bars for relative risks represent 95% CI.**

advancing age. Importantly, however, women did not attain the same incidence as men in old age, as reported[10,11]. Based on the present results, it is plausible that this difference in coronary heart disease incidence between men and women can be explained by the combination of differences in frequencies and relative risks of the ten coronary heart disease risk factors examined. In other words, based on our data it is not necessary to postulate additional factors, such as oestrogens to explain the sex difference in coronary heart disease incidence.

For both men and women aged 30 to 79 years at baseline, we found significant associations between coronary heart disease in seven out of the ten risk factors under study; however, the ranking and magnitude of risk differed in the two genders. In men, the magnitude of relative risks decreased from diabetes mellitus, hypertension, smoking, physical inactivity, no daily alcohol intake, hypercholesterolaemia through to obesity, while low or middle income, hypertriglyceridaemia, and lower school education did not confer increased risk in men. In women, the magnitude of relative risks decreased from diabetes mellitus, smoking, hypertension, physical inactivity, hypertriglyceridaemia, hypercholesterolaemia through to obesity, while low or middle income, lower school education, and no daily alcohol intake did not confer increased risk in women. In support of such sex differences, gender interacted with diabetes mellitus, smoking, no daily alcohol intake and hypertriglyceridaemia on coronary heart disease risk.

It is important to note that the observed association of coronary heart disease with each single risk factor is independent of the nine other risk factors, in models that included all ten risk factors. Because age was used as the underlying time scale, this was automatically adjusted for in the observed associations. This may partly explain why the magnitude of relative risk observed in a single risk factor in our study was relatively small, simply because the association was adjusted for variation in the other risk factors as well as for age. However, amongst the 10 risk factors there is considerable overlap. For example, hypercholesterolaemia and hypertriglyceridaemia are not independent, nor are they independent of obesity, alcohol consumption and diabetes status. The risk factor adjustment model may therefore underestimate the impact of an individual risk factor because of the impact of grouped associations of risk conditions (for example diabetes, obesity, and hyperlipidaemia).

In accordance with previous studies[11,12], diabetes mellitus was associated with the highest relative risk for coronary heart disease in both sexes and was most pronounced in women; the association was not significant in all age strata which was most likely due to lack of statistical power. Because of the low frequency, the attributable risk of diabetes mellitus was modest at 3% in both genders. We defined undiagnosed diabetes mellitus as non-fasting glucose $\geq 11{\cdot}1$ mmol . l^{-1}, which is most likely less strict than the current recommendation of fasting glucose ≥ 7 mmol . l^{-1}. Therefore, we may have underestimated the frequency of diabetes and consequently the attributable risk for diabetes. Smoking was associated with a high relative as well as a population-attributable risk for coronary heart disease in both sexes and all age groups. Smoking conferred a higher relative risk in women than in men, confirming previous reports[13,14]. Hypertension was also associated with a high relative as well as a population-attributable risk in both sexes and all age groups. The importance of hypertension has been demonstrated repeatedly[15,16]. Of the 6834 individuals with blood pressure <140 mmHg and not using antihypertensive medication, 489 (7%) took diuretics or other medication for heart disease. It is therefore possible that some of these individuals would have had blood pressure ≥ 140 mmHg if not on these drugs, and consequently the frequency and population-attributable risk for hypertension could be slightly underestimated in our analyses.

Hypercholesterolaemia only increased the risk of coronary heart disease in men and women aged 30 to 54 years at baseline, and not in the middle aged or elderly. However, as age and hypercholesterolaemia did not interact on coronary heart disease risk in women, the risk conferred by hypercholesterolaemia overall may nevertheless apply to all age groups in women. In support of this, the effect of reducing cholesterol has also been documented in those above 55 years[17,18]. That hypertriglyceridaemia is associated with a higher relative risk of coronary heart disease in women than in men is already documented[19]. Because we used non-fasting rather than fasting triglyceride levels (and with the same cut-off level of 2 mmol . l^{-1}[6]), we most likely slightly overestimated the frequency of hypertriglyceridaemia, and consequently the attributable risk of this risk factor.

The previously reported protective effect of moderate alcohol intake on coronary heart disease[20] could in this study be confirmed in men, but not in women. Obesity increased coronary heart disease risk by a modest 20% in the individual; however, because of the high frequency in the population it was the fourth most important factor in the population at large. Other studies have also reported an increased risk of obesity in both men and women[21–23]. Low physical activity, that is 'almost entirely sedentary or performing light physical activity less than 2 h per week', was an important risk factor for coronary heart disease in the individual as well as for the population at large. Others have reported similar findings[24–28].

Socioeconomic factors were only of importance in men aged 65 to 79 years at baseline. There was a surprising interaction between school education and age on coronary heart disease risk: a lower risk of coronary heart disease was conferred by less school education in elderly men, but not in middle aged or younger men. Elderly men had an increased relative risk associated with low or middle income and conversely reduced risk associated with lower school education. This finding is somewhat surprising, particularly as former studies have demonstrated an inverse social gradient in coronary heart disease risk not restricted to the elderly[29,30]. The most likely explanation is therefore that this represents a chance finding, rather than a genuine association.

We only chose to include 10 risk factors; however, a number of other risk factors in addition could have affected our results. Examples of such risk factors are high density lipoprotein cholesterol, homocysteine and C-reactive protein levels, but these risk factors were unfortunately not measured in the Copenhagen City Heart Study in 1976–78. We chose to include risk factors mentioned in the Joint European Societies Recommendations as well as a number of other well described coronary heart disease risk factors[6,7,10–30].

Because our study is observational and not a randomized trial, we can demonstrate associations but not causal relationships. Nevertheless, it should be noted that our cohort is a random sample of men and women from the general population of Copenhagen, and that the attendance rate was high at 74% of those invited. We used dichotomized risk factors in the analyses, which have the advantage that it allows simple comparison and thus ranking of all risk factors. For continuous risk factors like cholesterol, triglycerides and blood pressure, the risks attributable to such factors are, however, continuous rather than dichotomous. Thus, the methods used may be less sensitive to the impact of these risk factors. This means that we do not explore in detail the dose-response of these ten risk factors on coronary heart disease risk. Furthermore, if the cut-off points for some of the risk factors were changed, it is likely that some of the risk factor ranking may also change. The information about smoking, hypertension and physical activity was obtained at baseline but clearly these factors may have changed during the 21 years of follow-up. As this was not taken into account in the present analyses, we may have underestimated the importance of these risk factors (or other risk factors that also could have changed during follow-up).

Conclusion

In conclusion, importance of coronary heart disease risk factors may differ for individuals, the community, and by sex and age. Consequently, prevention strategies should be tailored accordingly. This is an important point that needs to be considered by all health professionals involved in advising individuals, or the general population, on risk factor modification.

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