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Classical risk factors and their impact on incident non-fatal and fatal myocardial infarction and all-cause mortality in southern Germany

Results from the MONICA Augsburg cohort study 1984–1992

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Background The MONICA (Monitoring Trends and Determinants in Cardiovascular Diseases) project in Augsburg provides the first population-based cohort study in Germany to quantify the associations of the risk factors hypertension, hypercholesterolaemia and smoking with incident non-fatal and fatal myocardial infarction and all-cause mortality, and to assess their impact at the population level.

Methods The cohort comprises 1074 men and 1013 women aged 45–64 years; they were followed over 8 years from 1984–1992. In the men, there were 61 non-fatal and fatal myocardial infarctions and 92 all-cause mortality events over this period; in the women the number of deaths from all causes was 45. Incidence rates, hazard rate ratios, population attributable fractions and rate advancement periods were calculated.

Results Adjusting for confounders, the myocardial infarction hazard rate ratios for men with hypertension, or a total cholesterol/HDL-cholesterol ratio $\geq$5·5, or smoking $\geq$20 cigarettes/day, were 2·0 (95% CI 1·2–3·5), 2·9 (95% CI 1·7–5·0), and 2·7 (95% confidence interval (CI) 1·4–5·0), respectively. The risk factor combination total cholesterol/HDL cholesterol ratio $\geq$5·5 and cigarette smoking was particularly hazardous. The three risk factors contributed 65% of the burden of myocardial infarction in the population. The rate advancement period for myocardial infarction associated with hypertension, total cholesterol/HDL cholesterol ratio $\geq$5·5 or smoking $\geq$20 cigarettes/day was 8·3, 12·4 and 11·5 years, respectively. In women, these risk factors were similarly predictive of all-cause mortality. Comparing the cohort data from Augsburg with those of two occupational cohorts from Germany reveals higher absolute myocardial infarction risks in the Augsburg population; however, the relative risk estimates in the Augsburg and the two occupational cohorts were very similar.

Conclusion Our results confirm the important contribution of the classical risk factors to the risk of myocardial infarction and all-cause mortality in Germany. The results pertaining to the concept of rate advancement periods particularly demonstrate the great potential for prevention. **(Eur Heart J 1998; 19: 1197–1207)**

Key Words: Myocardial infarction, total mortality, risk factors, population attributable fraction, rate advancement period, cohort study.

Introduction

Since the landmark studies on coronary heart disease such as the Seven Countries Study[1], the Framingham Study[2], and the Pooling Project[3], the predictive role of hypertension, hypercholesterolaemia, and smoking has been confirmed repeatedly in a large number of geographically or ethnically diverse populations, as reviewed by Stamler[4]. There is remarkable consistency in these results, in terms of magnitude of the relative risks[5–8]. In Germany, two occupational cohort studies[9–12] have addressed the link between classical risk factors and coronary heart disease morbidity and mortality. The MONICA (Monitoring Trends and Determinants in Cardiovascular Diseases) Augsburg

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project[13] is the first population-based prospective cohort study in Germany to assess these links.

The present study describes the incidence rates and hazard rate ratios of non-fatal and fatal myocardial infarction and all-cause mortality by levels of the risk factors hypertension, hypercholesterolaemia, and smoking in a cohort of middle-aged men and women. This includes consideration of covariates or potential confounders such as alcohol intake, obesity, diabetes, and education. In addition, because the study was population-based it enabled the impact of hypertension, hypercholesterolaemia and smoking to be estimated in terms of their population attributable fraction and the respective rate advancement periods.

Study population and methods

MONICA Augsburg Survey 1984–85

The designs of the multinational WHO MONICA project[14,15] and the MONICA Augsburg project have been described elsewhere[13,16]. The study area of the MONICA Augsburg project in 1984 comprised the city of Augsburg and the Landkreise Augsburg and Aichach-Friedberg districts, covering a population of 532 987 inhabitants. A random sample of 5312 persons of German nationality was drawn from the population of 282 279 inhabitants aged 25–64 years[16,17].

The data were gathered through interview and physical examination. 79·3% responded, i.e. 4022 of the 5069 eligible people (5312 minus those who had died after sampling, minus errors in the population register, etc.) participated in the survey. The cohort study analyses were restricted to the 45–64 year age range at baseline comprising 2087 individuals (1074 men and 1013 women).

Morbidity and mortality follow-up 1984–1992

The follow-up was conducted from 1984 to 1992 and assessed non-fatal and fatal myocardial infarction and all-cause mortality (vital status) over a median period of 7·9 and a maximal period of 8·2 years. We were able to use the MONICA Augsburg coronary event registry to assess non-fatal and fatal myocardial infarction because, as a population-based registry, it covers the population from which the sample of the 1984–85 survey was drawn. The registry monitors non-fatal and fatal myocardial infarction outside and inside hospitals of the study area. Detailed descriptions of the procedures and quality of the data of the MONICA Augsburg coronary event registry have been published[13,18,19].

The WHO MONICA diagnostic categories (derived from ECG, enzyme, symptom, and necropsy findings) included as myocardial infarction events in this cohort study are (1) definite and possible non-fatal acute myocardial infarction and (2) fatal coronary heart disease (combining definite and possible fatal coronary events and fatal cases with insufficient data). Detailed descriptions of the definitions and applications of these diagnostic categories have been published[14,15]. We considered a myocardial infarction as incident if it was the first event during follow-up in a person reporting no history of heart attack in the 1984–85 survey. Mortality was ascertained by regularly checking the vital status of all cohort members through the population registries inside and outside the study area; this procedure guaranteed that the vital status of cohort members who had moved out of the study area could also be assessed. During the follow-up, only six persons were lost (99·7% completeness). Death certificates were obtained from the local health departments and were coded for the underlying cause of death by a single trained person using the 9th revision of the International Classification of Diseases (ICD-9). In three cases (2%) the cause of death was missing.

For the analyses of all-cause mortality, we excluded 20 of the 1074 men because of missing data on the risk factors total cholesterol, HDL-cholesterol, cigarette smoking, and on the potential confounders alcohol intake, body mass index, diabetes mellitus and education. The remaining 1054 men provided 8014 person years, with a median follow-up time of 7·9 years; 92 deaths accumulated over this time. Of the 1013 women, 996 had complete data on all relevant variables and provided 7764 person years over a median follow-up of 7·9 years; 45 deaths occurred over this follow-up period.

For the analyses of incident non-fatal and fatal myocardial infarction, we excluded 43 men who reported a heart attack at baseline, and also excluded 16 men with missing data on risk factors or potential confounders, leaving 1015 men with 7507 person years and a median follow-up time of 7·9 years; 61 incident myocardial infarctions developed over this period. The 32 men who moved outside the study area during follow-up were censored at the date of the move. Analyses of incident myocardial infarction were not feasible in women due to the small number of events.

Determination and categorization of risk factors

Systolic and diastolic blood pressure were measured three times in sitting subjects with the Hawksley Random Zero Sphygmomanometer[20] under standardized conditions[21,14]. All blood pressure values are based on the first and fifth phase of the Korotkoff sounds and on the calculation of the mean of the second and third blood pressure measurements. Subjects aware of hypertension, taking medication against hypertension and/or having blood pressure values $\geq$160 mmHg systolic or $\geq$95 mmHg diastolic were defined as having actual hypertension. For the descriptive analyses, this group

was subdivided into treated and untreated hypertensives. A systolic blood pressure between 140 and 159 mmHg and/or diastolic blood pressure between 90 and 94 mmHg in the absence of treatment for hypertension was defined as borderline hypertension.

Non-fasting blood samples were drawn under standardized conditions[17]. Serum total cholesterol and HDL-cholesterol analyses were carried out with an autoanalyser by a clinical laboratory (Zentralklinikum Augsburg, Germany). An enzymatic method (CHOD-PAP; Boehringer Mannheim, Germany) was applied; HDL-cholesterol was precipitated with phosphotungstate/Mg^{2+}. Internal and external quality control was performed according to the WHO MONICA Manual[14]. The total cholesterol/HDL-cholesterol ratio was derived and categorized as <4·0, 4·0–5·4 and ≥5·5.

Smoking was ascertained with a questionnaire that asked about current and former smoking status and number of cigarettes currently smoked per day. Male smokers were subdivided into those smoking <20 cigarettes/day and those smoking ≥20 cigarettes/day. For women, we defined two groups of smokers, namely <11 cigarettes/day and ≥11 cigarettes/day. For some analyses, smoking was simply dichotomized as all current smokers vs all never and former smokers.

Determination and categorization of potential confounders

Assessment of alcohol intake was based on questionnaire data regarding weekday and weekend consumption of beer, wine, and spirits and has been described in detail elsewhere[22,23]. Alcohol intake was categorized into five groups in men: non-drinkers, 0·1–19·9, 20–39·9, 40–79·9, ≥80 g . day^{-1}; the last three categories were combined into ≥20 g . day^{-1} for women because of their lower alcohol intake. For determination of body weight and height, participants were asked to remove shoes and heavy clothing. Body mass index was calculated as weight/height^2 (kg . m^{-2}) and categorized as <25, 25–29·9, ≥30 kg . m^{-2}. Diabetes was ascertained by self-reporting. Educational attainment was estimated by recording years of schooling completed. The variable was then dichotomized into <10 years and ≥10 years. While age was included as a continuous variable, all categorical variables were included as design variables in statistical models.

Statistical methods

Descriptive statistics (means, standard deviations, and proportions) for men and women were calculated for the risk factors and some baseline characteristics. The study population and incidence rates were stratified by the several categories of each risk factor.

Age-adjusted incidence rates per 1000 person years were calculated for each risk factor level separately for men and women. Age-adjustment was by direct standardization, using the 1980 West German population as the standard. Age-adjusted hazard rate ratios were derived from multivariable Cox proportional hazards models[24], reflecting the hazard in the exposed vs the unexposed, and should be interpreted as relative risks.

To evaluate the independent contribution of the three risk factors hypertension, smoking, and hypercholesterolaemia, multivariable Cox proportional hazards models were employed. Each outcome (myocardial infarction incidence in men, all-cause mortality in men, all-cause mortality in women) was modelled separately, and each model contained all relevant risk factors simultaneously and controlled for age and the other potential confounders, as specified in the preceeding section. The assumption of proportionality of hazards was assessed by fitting models stratified by risk factor levels, then plotting the log(-log(survival)) curves to check parallelism[25]. No severe deviations from parallelism were evident.

To study the effect of each risk factor individually and jointly on its potential to cause myocardial infarction, the male population was completely cross-classified with respect to the dichotomized traits, actual hypertension, smoking and total cholesterol/HDL cholesterol ratio ≥5·5. This yielded eight mutually exclusive risk factor combinations. Age-adjusted incidence rates of myocardial infarction in men were computed as described. Age-adjusted hazard rate ratios were derived from one model which contained seven design variables, one for each of the seven risk factor combinations.

Accordingly, we calculated the category-specific population attributable fraction of myocardial infarction (also known as the population attributable risk percent)[26]. The population attributable fraction of myocardial infarction is defined as the proportion of all cases of myocardial infarction that is attributable to the exposure occurring in a population of both exposed and unexposed individuals[27]. The formula used was Σ_i (p_i ($RR_i - 1$)/RR_i) where p_i is the proportion of total myocardial infarction cases in the population which developed in the i-th exposure category[27]. RR_i represents the relative risk or hazard rate ratio for the i-th exposure category.

Rate advancement periods for non-fatal and fatal myocardial infarction were calculated according to Brenner *et al.*[28]. Similar to the concept of years of potential life lost, this measure expresses the public health impact of a risk factor as the average number of (healthy) life years a person with a certain risk factor loses due to the premature onset of disease when compared to a person without the respective risk factor. In more technical terms, the rate advancement period expresses an age difference A_0-A_1, where A_0 is the earliest age at which the unexposed are expected to have the same rate of myocardial infarction that the exposed

are expected to have at age A_1. Computationally, the rate advancement period is derived by dividing the beta coefficient of the exposure variable in a Cox proportional hazards model by the beta coefficient of the continuous age variable.

The rate advancement period may also be interpreted as the average time period by which a certain rate of myocardial infarction is advanced or prematurely reached in subjects exposed to a risk factor (e.g. hypertension vs normotension; total cholesterol/HDL cholesterol ratio ≥5·5 vs <5·5, smoking vs non-smoking). In other words, individuals with a total cholesterol/HDL cholesterol-ratio ≥5·5 exhibiting a certain rate of myocardial infarction at age A_1 would have been expected to have had that same rate only at age $A_0 > A_1$ (the difference in the MONICA Augsburg cohort being 12·4 years) had they been unexposed (total cholesterol/HDL cholesterol ratio <5·5) and given that all other covariates are identical and assuming the absence of competing risks. In our study, the rate advancement periods were based on parameters estimated from the multivariable Cox proportional hazards model that additionally adjusted for potential confounders.

Results

Baseline characteristics of the study population

The average age of the study population was 54 years. Men and women did not differ with respect to the mean body mass index (27·7 kg . m^{-2}). Men tended to have a slightly higher average systolic and diastolic blood pressure (137 vs 135 mmHg; 84 vs 82 mmHg, respectively) and a lower total (6·33 vs 6·43 mmol . l^{-1}) and HDL-cholesterol (1·32 vs 1·61 mmol . l^{-1}) than women. Table 1 displays the prevalence of the categorized risk factors. The prevalence of actual hypertension was very similar in men and women; the treatment status was better in women than in men. The total cholesterol categories were distributed fairly evenly in men and in women. While more than one third (36·5%) of men had a total cholesterol/HDL cholesterol ratio ≥5·5, only 15·9% of women exhibited values equal or above this ratio. The proportion of never-smokers was substantially higher in women than in men, whereas heavy smoking was clearly more common in men. Men more often reported a history of a previous heart attack (3·7% vs 0·8%). Table 2 shows the prevalence of categories of potential confounders at baseline. Alcohol intake was markedly higher in men than in women. While the distribution of body mass index categories was different between men and women, the prevalence of self-reported diabetes mellitus did not differ substantially across gender. A significantly higher proportion of women than men reported low education levels.

Table 1 Prevalence (%) of risk factor categories at baseline. MONICA Augsburg cohort study 1984–1992

	Men (n = 1054)	Women (n = 996)
Hypertension		
normotensive	50·2	56·9
borderline (140–159/90–94 mmHg)	23·9	17·3
untreated (≥160/95 mmHg)	16·0	10·6
treated with medication	9·9	15·2
actual hypertension (treated + untreated)	25·9	25·8
Total cholesterol		
<5·17 mmol . l^{-1} (<200 mg . dl^{-1})	16·5	14·6
5·17–6·46 mmol . l^{-1} (200–249 mg . dl^{-1})	41·4	39·4
6·47–7·75 mmol . l^{-1} (250–299 mg . dl^{-1})	30·6	32·7
≥7·76 mmol . l^{-1} (≥300 mg . dl^{-1})	11·5	13·4
HDL-cholesterol		
<1·03 mmol . l^{-1} (<40 mg . dl^{-1})	23·2	8·2
1·03–1·28 mmol . l^{-1} (40–49 mg . dl^{-1})	30·3	15·0
1·29–1·54 mmol . l^{-1} (50–59 mg . dl^{-1})	23·1	24·9
1·55–1·80 mmol . l^{-1} (60–69 mg . dl^{-1})	13·0	22·2
≥1·81 mmol . l^{-1} (≥70 mg . dl^{-1})	10·3	29·7
Total cholesterol/HDL-cholesterol ratio		
≥5·5	36·5	15·9
4·0–5·4	36·9	33·2
<4·0	26·6	50·9
Cigarette smoking		
never	25·0	73·7
former	42·3	12·8
<11 cigarettes/day	10·8	7·6
11–19 cigarettes/day	6·0	2·3
≥20 cigarettes/day	15·9	3·6
current smoking	32·7	13·5

Table 2 Prevalence (%) of categories of potential confounders at baseline. MONICA Augsburg cohort study 1984–1992

	Men (n = 1054)	Women (n = 996)
Alcohol intake		
non-drinkers	13·2	44·0
1–19 g . day^{-1}	21·3	36·2
20–39 g . day^{-1}	24·0	15·6
40–79 g . day^{-1}	31·0	3·6
≥80 g . day^{-1}	10·4	0·6
Body mass index (BMI)		
<25 kg . m^{-2}	19·8	31·7
25–29·9 kg . m^{-2}	58·3	41·7
≥30 kg . m^{-2}	21·9	26·6
Diabetes mellitus (positive self-report)	4·8	4·0
Education (<10 years)	13·1	40·7

Classical risk factors and incident non-fatal and fatal myocardial infarction in men

Figure 1 depicts the age-adjusted incidence rates and age-adjusted hazard rate ratios (relative risks) of non-fatal and fatal myocardial infarction by risk factor levels in men. Across the categories normotensive, borderline, untreated hypertension, and treated hypertension, a

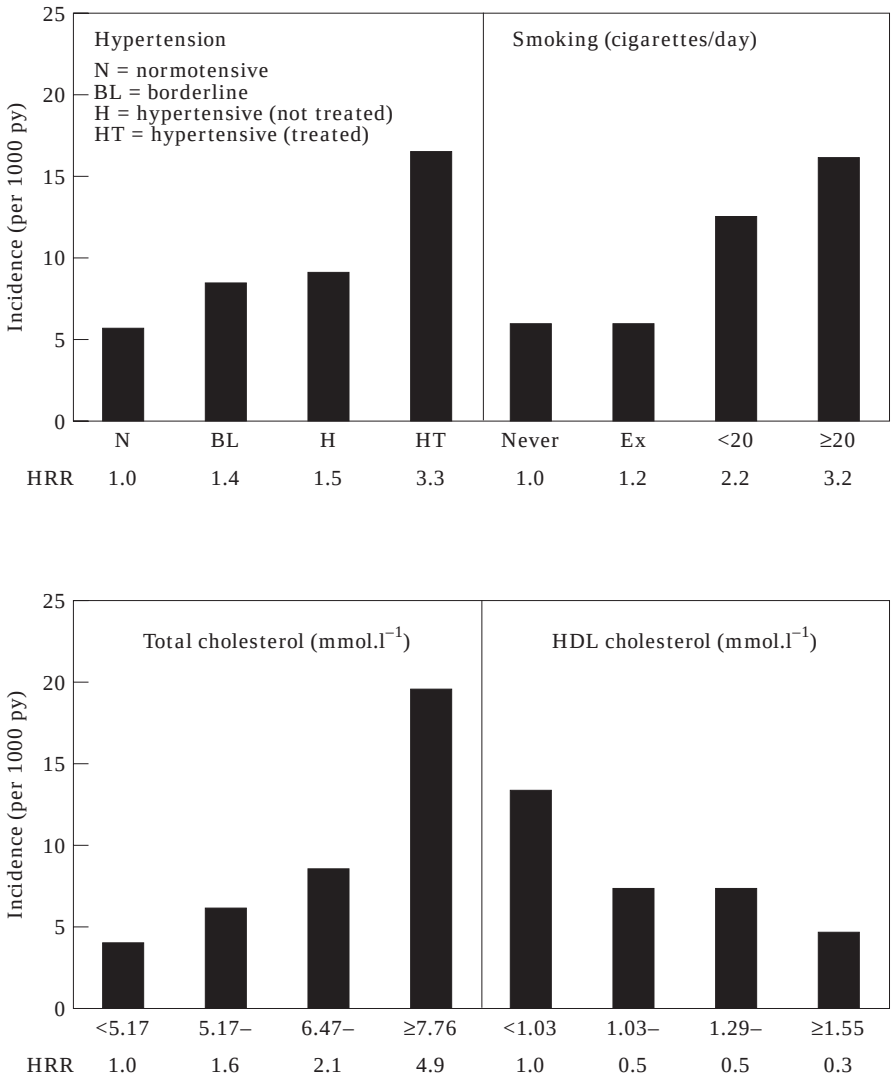


Figure 1 **Age-adjusted incidence rates and age-adjusted hazard rate ratios (HRR) of non-fatal and fatal myocardial infarction (MI) by risk factor levels, men.**

stepwise increase in age-adjusted myocardial infarction incidence rates was observed with increasing severity of hypertension. The age-adjusted myocardial infarction incidence rates ranged from 5·7 cases per 1000 person years among normotensives to 16·4 per 1000 person years among individuals treated for hypertension. Never smokers and former smokers had the same myocardial infarction incidence rates (5·7 per 1000 person years) which rose substantially with increasing intensity of smoking. Likewise, the myocardial infarction incidence rates rose with increasing total cholesterol levels, peaking at levels of $\geq 7{\cdot}76$ mmol . l^{-1} (≥ 300 mg . dl^{-1}) (19·5 per 1000 person years). In contrast, HDL-cholesterol levels showed an inverse relationship with incidence of myocardial infarction. The age-adjusted hazard rate ratios of myocardial infarction shown for the respective risk factor levels basically mirror the incidence rates (Fig. 1).

Table 3 shows the independent association of actual hypertension, total cholesterol/HDL cholesterol ratio, and smoking with incident myocardial infarction in men, derived from one multivariable model including all predictors simultaneously and adjusting for age, alcohol intake, body mass index, diabetes, and educational attainment, as specified in the methods section. Actual hypertension was associated with a two-fold increase in risk of myocardial infarction while a total cholesterol/HDL cholesterol ratio $\geq 5{\cdot}5$ and smoking ≥ 20 cigarettes/day approximately tripled the risk.

Classical risk factors and all-cause mortality in men

Figure 2 shows age-adjusted all-cause mortality rates and age-adjusted hazard rate ratios of all-cause

Table 3 Incident myocardial infarction hazard rate ratios (HRR) (and 95% confidence intervals) for men with a classical risk factor relative to those without the risk factor*. MONICA Augsburg cohort study 1984–1992

	HRR	95% CI
Actual hypertension (yes vs no)	2·0	1·2–3·5
Total cholesterol/HDL-cholesterol ratio ($\geq$5·5 vs <5·5)	2·9	1·7–5·0
Cigarette smoking		
never/former	1·0	
<20 cigarettes . day^{-1}	1·8	1·0–3·5
$\geq$20 cigarettes . day^{-1}	2·7	1·4–5·0

*Results are based on a model including all predictors simultaneously and adjusting for age, alcohol intake, body mass index, diabetes, educational attainment. (See statistical methods for details.)

mortality by risk factor levels in men. The risk of dying increased from normotensive to borderline to hypertensive; untreated hypertensives and those on antihypertensive drugs had similar high rates of all-cause mortality (16·3 and 14·8 per 1000 person years). A clear dose–response relationship existed between smoking and all-cause mortality, rising from 'never' over 'former smokers' to 'smokers of <20 cigarettes/day' and $\geq$'20 cigarettes/day'. A U-shaped relationship was observed for total cholesterol and HDL-cholesterol with all-cause mortality, with the lowest rates in men of 5·17–6·47 mmol . l^{-1} (200–249 mg . dl^{-1}) and 1·03–1·29 mmol . l^{-1} (40–49 mg . dl^{-1}). The effect of the different statistical adjustment methods — standardization of rates versus model-based adjustment of the hazard rate ratios — was reflected in the higher hazard rate ratios for treated hypertensives.

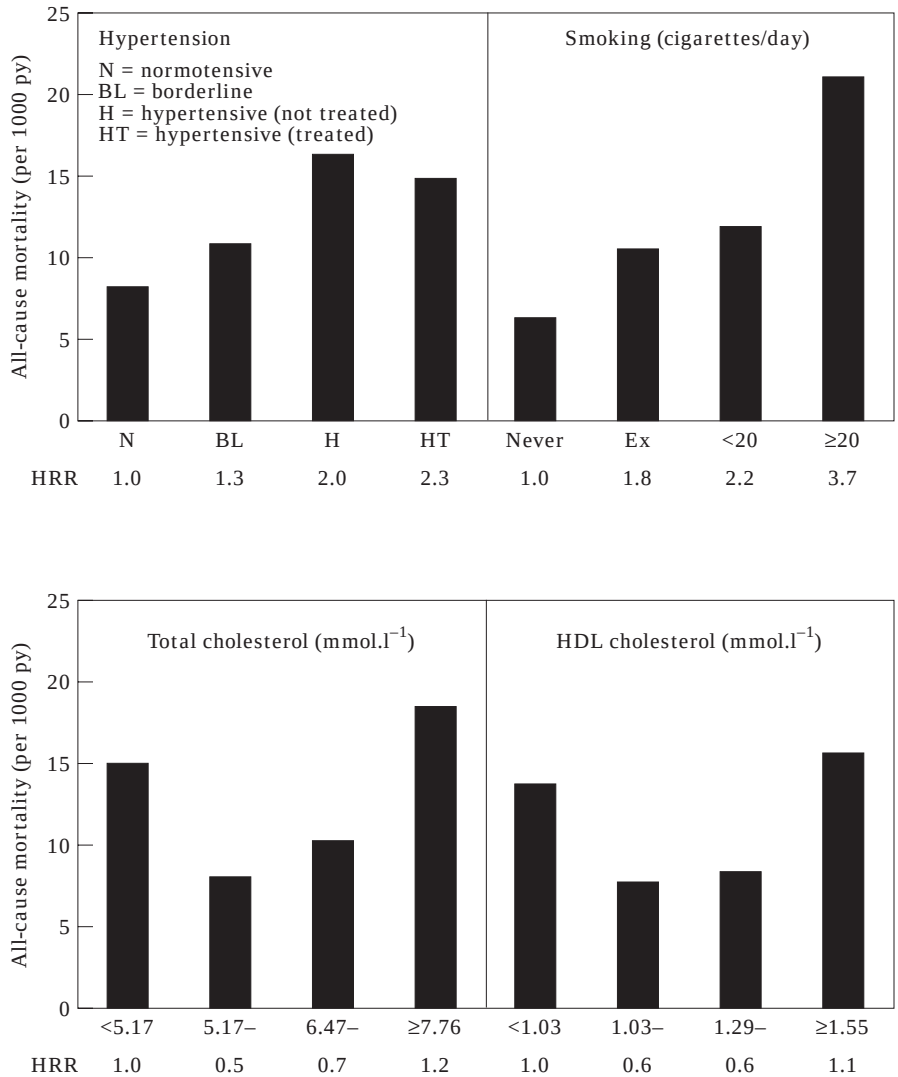


Figure 2 **Age-adjusted all-cause mortality rates and age-adjusted hazard rate ratios (HRR) of all-cause mortality by risk factor levels, men.**

Table 4 All-cause mortality hazard rate ratios (HRR) (and 95% confidence intervals) for men with a classical risk factor relative to those without the risk factor*. MONICA Augsburg cohort study 1984–1992

	HRR	95% CI
Actual hypertension (yes vs no)	2·1	1·4–3·3
Total cholesterol/HDL-cholesterol ratio		
<4·0	2·5	1·4–4·5
4·0–5·4	1·0	
≥5·5	2·3	1·3–4·0
Cigarette smoking		
never	1·0	
former	1·7	0·9–3·5
<20 cigarettes/day	2·2	1·0–4·8
≥20 cigarettes/day	2·9	1·4–6·1

*Results are based on a model including all predictors simultaneously and adjusting for age, alcohol intake, body mass index, diabetes, educational attainment. (See statistical methods for details.)

The independently predictive role of the classical risk factors for all-cause mortality in men is depicted in Table 4. Actual hypertension doubled the risk of all-cause mortality independent of total cholesterol/HDL cholesterol ratio and smoking, and adjusting for previously specified potential confounders. To reflect the strong U-shaped relationship between both total and HDL-cholesterol and all-cause mortality, the total cholesterol/HDL cholesterol ratio was divided into three categories. Both a total cholesterol/HDL cholesterol ratio lower than 4·0 and a ratio of 5·5 or more were associated with a substantially increased risk of death. In contrast to never-smokers, former smokers had an increased risk for all cause-mortality (not for myocardial infarction) which was surpassed by smokers who smoked <20 cigarettes/day (hazard rate ratio 2·2, 95% CI 1·0–4·8) and those who smoked ≥20 cigarettes/day (hazard rate ratio 2·9, 95% CI 1·4–6·1). The multivariable approach used here clearly attenuated the hazard rate ratio associated with the ≥20 cigarettes/day category (compared to the age-only-adjusted hazard rate ratio for smoking ≥20 cigarettes/day in Fig. 2).

Classical risk factors and all-cause mortality in women

Figure 3 depicts the age-adjusted all-cause mortality rates and age-adjusted hazard rate ratios of all-cause mortality by risk factor levels in women. Across the blood pressure categories, the highest all-cause mortality rates were observed in treated hypertensives.

A detrimental effect of smoking was only observed in women who smoked ≥11 cigarettes/day. While mortality rates did not increase over the lower total cholesterol range (<7·76 mmol . l^{-1}), women with total cholesterol levels of 7·76 mmol . l^{-1} (300 mg . dl^{-1}) or more had the highest mortality rates. There was a weak indication of a U-shaped relationship between HDL-cholesterol and all-cause mortality. Table 5 reveals that of the three classical risk factors, actual hypertension was independently associated with a two-fold higher risk of all-cause mortality, as was a total cholesterol/HDL cholesterol ratio ≥5·5. The effect estimate for smoking indicated a detrimental effect of smoking ≥11 cigarettes/day (hazard rate ratio 1·7, 95% CI 0·5–5·6), but did not reach statistical significance.

Classical risk factors, their combinations and incidence of non-fatal and fatal myocardial infarction

Only 37% of the men exhibited none of the three risk factors, 39% one risk factor, and 24% two or more risk factors. Eighty-seven percent of myocardial infarction cases had one or more risk factors and 54% two or more risk factors simultaneously at baseline. Age-adjusted incidence rates of non-fatal and fatal myocardial infarction were calculated in men by the dichotomized risk factors and their combinations. Figure 4 shows that as the number of risk factors increased, so did the rates of myocardial infarction and, likewise, the age-adjusted hazard rate ratios. Individuals with a single risk factor had lower incidence rates and hazard rate ratios of myocardial infarction than those having two or more risk factors. Individuals who were hypertensive, hypercholesterolaemic and cigarette smokers had the highest risk of myocardial infarction (hazard rate ratio = 11·1).

Population attributable fraction

Based on the same Cox proportional hazards model discussed in the previous section (Fig. 4), we calculated the population attributable fraction of incident myocardial infarction due to actual hypertension, total cholesterol/HDL cholesterol ratio ≥5·5, and smoking. Taken together, these three risk factors contributed 65% to the disease burden of myocardial infarction in the study population. Two specific risk factor combinations, namely smoking and a total cholesterol/HDL cholesterol ratio ≥5·5, and all three risk factors combined are responsible for half (32%) of the population attributable fraction.

Rate advancement periods

Table 6 shows rate advancement periods calculated for incident non-fatal and fatal myocardial infarction and based on the multivariable model described in the statistical methods section and presented in Table 3. Actual hypertension and smoking ≥20 cigarettes/day were associated with rate advancement periods of 8·3 and 11·5 years, respectively. A total cholesterol/HDL

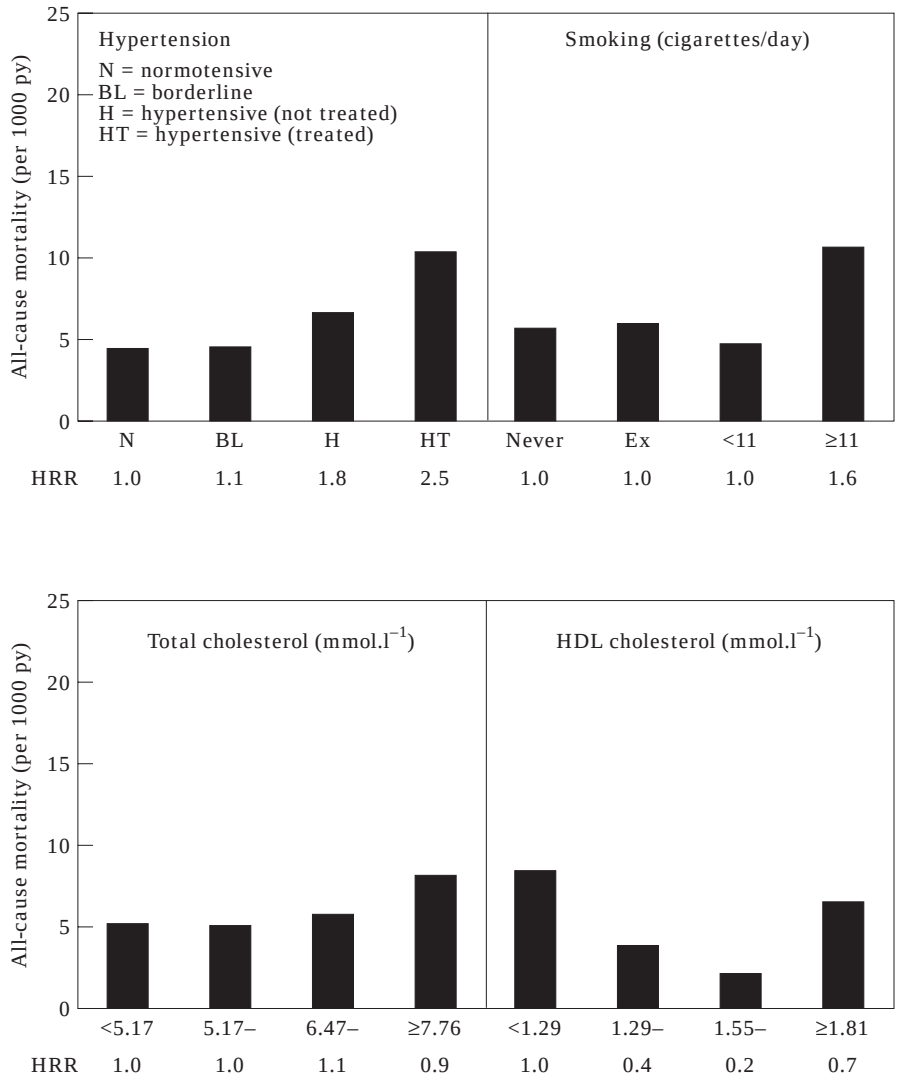


Figure 3 **Age-adjusted all-cause mortality rates and age-adjusted hazard rate ratios (HRR) of all-cause mortality by risk factor levels, women.**

cholesterol ratio ≥5·5 was associated with a rate advancement period of 12·4 years.

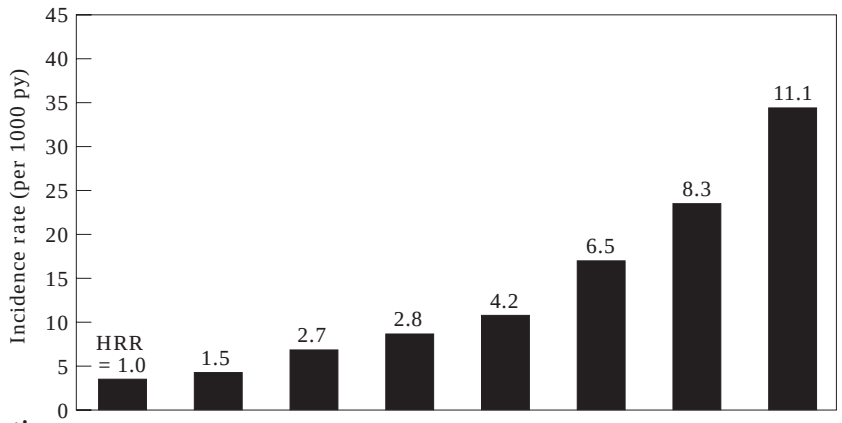
Discussion

The results of this study confirm the important role of the risk factors hypertension, hypercholesterolaemia, and smoking on the risk of non-fatal and fatal myocardial infarction and all-cause mortality in a population of middle-aged men in Germany. The associations between these risk factors and all-cause mortality were similar in women, even though the small number of deaths occurring over the 8 year follow-up period do not allow solid conclusions for the female population studied here. For example, the association of current regular smoking with all-cause mortality did not reach statistical significance, probably due to the small number

Table 5 All-cause mortality hazard rate ratios (HRR) (and 95% confidence intervals) for women with a classical risk factor relative to those without the risk factor*. MONICA Augsburg cohort study 1984–1992

	HRR	95% CI
Actual hypertension (yes vs no)	2·0	1·1–3·7
Total cholesterol/HDL-cholesterol ratio (≥5·5 vs <5·5)	2·3	1·2–4·4
Cigarette smoking		
never/former	1·0	
<11 cigarettes/day	1·0	0·3–3·3
≥11 cigarettes/day	1·7	0·5–5·6

*Results are based on a model including all predictors simultaneously and adjusting for age, alcohol intake, body mass index, diabetes, educational attainment. (See statistical methods for details.)



Risk factor combination:								
Actual hypertension	0	0	1	0	1	1	0	1
TC/HDL-C ≥ 5.5	0	0	0	1	1	0	1	1
Smoking (≥ 1 cig./day)	0	1	0	0	0	1	1	1
Incident MIs/ Population at risk:	8/373	4/133	7/110	9/149	7/75	4/35	16/107	6/33

Figure 4 **Age-adjusted incidence rates and age-adjusted hazard rate ratios (HRR) of non-fatal and fatal myocardial infarction (MI) in men by the individual risk factors hypertension, total cholesterol/ HDL cholesterol ≥5·5, cigarette smoking and by combinations of these risk factors.**

of women smoking (and less cigarettes/day) and the smaller number of deaths in women of this age group.

In the MONICA Augsburg cohort, the relationship of total and HDL-cholesterol with all-cause mortality rates in men was markedly U-shaped, indicating an increased risk of death both at the upper and at the lower end of the cholesterol distribution. Why this observation has been made repeatedly but not consistently[29,30,12] is not clear[31]. Iribarren *et al.*[29] have shown that differences in health-related baseline characteristics and subclinical preexisting disease can explain a substantial proportion of excess all-cause mortality associated with low total cholesterol levels. In the study by Iribarren *et al.* the U-shaped relationship was restricted to men with at least one risk factor. Gaziano *et al.*[32] have suggested that the link between an increased risk of death and low total cholesterol levels observed primarily in population-based but not in occupational cohort studies may be explained by the higher prevalence of pre-morbid conditions in the less healthy population-based studies vs the healthier occupational populations.

To evaluate the absolute level of myocardial infarction risk experienced in our population-based cohort, we compared our incidence rates to two occupational cohorts, which provide incidence rates of myocardial infarction in Germany. The GRIPS study (Göttinger Risiko,- Inzidenz- und Prävalenzstudie) comprises a cohort of about 5300 employees aged 40–59 years free of heart disease at baseline who were working in the area of Göttingen in 1982[10]. The PROCAM (Prospective Cardiovascular Münster) Study, followed since 1979 roughly 4500 disease-free men aged 40–65 years who were employed in various companies in the region of Münster[11,12]. As expected, the incidence rates of our population-based cohort, which comprises employed as well an unemployed participants, were higher than those of both occupational German cohorts. For example, standardizing the published 5-year cumulative incidence rate of the GRIPS cohort[9] to the MONICA Augsburg cohort age distribution (using the weights 0·3524, 0·3181, 0·3295 for the 5-year age groups between 45 and 59 years) revealed a substantially lower 5-year cumulative myocardial infarction incidence of 28·2 cases per 1000 persons than the 5-year incidence rate of 40·7 per 1000 persons in the MONICA Augsburg cohort. The difference with the PROCAM cohort was less pronounced as their 5-year cumulative incidence rate was 38·9 per 1000 (Assmann and Schulte, personal communication). The higher overall risk of myocardial infarction in the MONICA Augsburg cohort can be attributed to an almost two-fold higher myocardial infarction incidence rate in 55–59 year-old-men, an age

Table 6 Rate advancement periods (RAP) in years of non-fatal and fatal myocardial infarction in men for the classical risk factors relative to those without the respective risk factor*. MONICA Augsburg cohort study 1984–1992

	RAP (years)
Actual hypertension (yes vs no)	8·3
Total cholesterol/HDL-cholesterol ratio (≥5·5 vs <5·5)	12·4
Cigarette smoking	
<20 cigarettes/day	7·1
≥20 cigarettes/day	11·5

*Results are based on a model including all predictors simultaneously and adjusting for age, alcohol intake, body mass index, diabetes, educational attainment. (See statistical methods for details.)

category in which the healthy worker effect in the occupational cohorts becomes increasingly manifest.

Given these differences in levels of background risk, it is noteworthy that the estimates of relative risk in the MONICA Augsburg cohort and the occupational cohorts were very close[11,9]. For example, the risk ratios of incident myocardial infarction for any current smoking were reported in GRIPS as 2·1, in PROCAM as 2·4 compared to hazard rate ratios of 1·8 for smoking <20 cigarettes/day and 2·7 for smoking ≥20 cigarettes/day in our cohort. Similarly, for hypertension, the risk ratio of 2·2 for incident myocardial infarction in the GRIPS cohort, 2·1 in the PROCAM cohort and 2·0 in the MONICA Augsburg cohort compare well. The important role of total and HDL-cholesterol in the development of incident myocardial infarction was similarly confirmed in these three German cohort studies. In addition, the pattern of hazard rate ratios of myocardial infarction observed in the MONICA Augsburg cohort were very similar to those reported in a Finnish cohort followed over 12 years, which focused on the risk factors smoking, elevated serum total cholesterol and elevated blood pressure[33].

To illustrate the impact of the risk factors studied here, rate advancement periods were calculated[28]. As described in the statistical methods section, this measure expresses the public health impact of a risk factor and is similar to the concept of years of potential life lost. In the MONICA Augsburg cohort, the rate advancement periods for the classical risk factors ranged from 7 to 12 years, which points towards a great public health impact of these risk factors. The rate advancement periods of 7·1 and 11·5 years for smoking <20 cigarettes/day and ≥20 cigarettes/day, respectively, observed in the MONICA Augsburg cohort compare well with those which we calculated from a recent GRIPS publication[10]: smoking (any current regular smoking vs never/former) in this study was associated with a 10 year rate advancement period.

Focusing on the joint contribution of risk factors, we found that hypertension, a total cholesterol/HDL cholesterol ratio ≥5·5 and smoking exerted a synergistic effect on the risk of myocardial infarction in men. The incidence rates of myocardial infarction observed for the combinations hypertension and smoking, total cholesterol/HDL cholesterol ratio ≥5·5 and smoking, and all three risk factors combined clearly exceeded the expected rates (based on the sum of the individual rates).

Sixty-five percent of the disease burden of myocardial infarction in our population was due to the risk factors hypertension, hypercholesterolaemia, and smoking. In this setting, the population attributable fraction is a highly appropriate measure since myocardial infarction is indeed a preventable disease, the causal relationship of the classical risk factors with myocardial infarction is well established and it is conceivable that these risk factors can be eliminated. Our findings are almost identical to those of Jousilahti *et al.*[33] and underscore the particularly detrimental effect of the risk factor combination smoking and hypercholesterolaemia.

The public health impact of these risk factors is considerable and warrants attention by policy makers and health professionals alike. However, the individual and structural barriers to risk factor modification should not be underestimated; in light of the recent results from EUROASPIRE[33,34] it becomes clear that even in patients who survived a myocardial infarction, risk factor modification is not an easy task. However, our results from the MONICA Augsburg cohort and especially those pertaining to the concepts of population-attributable fraction and rate advancement periods clearly demonstrate the great potential for prevention by controlling the classical risk factors at the population level.

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