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Clinical research

Prognostic value of apolipoprotein B and A-I in the prediction of myocardial infarction in middle-aged men and women: results from the MONICA/KORA Augsburg cohort study

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Prognostic value

Aims To investigate the association between apolipoprotein B (apoB), A-I (apoA-I), the apoB/apoA-I ratio, and the incidence of coronary events.
Methods and results Analysis included 1414 men and 1436 women aged 35–64 years without a prior coronary event who participated in the population-based MONICA Augsburg survey 1984–85 (median followed-up period 13 years). Incidence of fatal and non-fatal myocardial infarction, and sudden cardiac death was assessed using data of the MONICA/KORA Augsburg coronary event registry. During follow-up, 114 incident coronary events occurred in men and 31 in women. In multivariable analysis, an increase of 1 standard deviation in the serum concentration of apoB was associated with an increased risk of coronary events in men [hazard ratio (HR) = 1.49; 95% confidence interval (CI); 1.25–1.78] and in women (HR = 1.73; 95% CI; 1.32–2.27). By contrast, elevated concentrations of apoA-I were not associated with a significantly decreased risk of coronary events in either sex (HR = 0.91). Furthermore, the predictive power of the apoB/apoA-I ratio was similar to that of the total cholesterol/HDL cholesterol ratio in men and women.
Conclusion ApoB and the apoB/apoA-I ratio were strong predictors of coronary events in middle-aged men and women, whereas apoA-I did not add significantly to the estimation of future coronary risk.

Introduction

Elevated total cholesterol (TC), the TC/HDL cholesterol ratio, LDL-cholesterol, and low HDL-cholesterol are well established risk factors for coronary heart disease (CHD).[1–3] Of these risk factors, the TC/HDL cholesterol ratio has been shown to be the most effective discriminator of CHD risk.[1,3] However, there is increasing evidence that the measurement of apolipoprotein B (apoB), the moiety of LDL, and apolipoprotein A-I (apoA-I), the protein component of HDL may add valuable information in the clinical assessment of susceptibility to CHD.[4–9]

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Whether apolipoproteins provide any additional predictive information over and above the usual lipid measurements remains controversial to date. Some early case–control studies found apoB and apoA-I to be better predictors of CHD than the usual lipids.[10,11] This idea was supported by several later cohort studies.[12,13] However, other prospective studies did not confirm these findings.[14,15] Recently, results from one of the largest studies to investigate these factors, the Apolipoprotein-related Mortality Risk (AMORIS) study were published demonstrating that the concentrations of apoB and apoA-I, as well as the ratio of apoB to apoA-I, improved prediction of CHD risk.[16]

In the present prospective study, we therefore investigated whether apoB, apoA-I, and the apoB/apoA-I ratio are independent risk factors for incident coronary events and whether these apolipoproteins are superior to the usual lipoprotein measurements in the assessment of CHD risk in a representative sample of middle-aged German men and women.

Materials and methods

Study population

The MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) Augsburg project was part of the multinational WHO MONICA project, and the design of the project has been described in detail elsewhere.[17] The data source used in the present analysis was the first cross-sectional survey of the MONICA Augsburg project conducted between October 1984 and June 1985. Only German citizens between 25 and 64 years of age were included. The study participants comprised 4 022 men and women (response rate 75.7%). The present analysis was restricted to persons aged 35–64 years without a prior myocardial infarction (MI) at baseline examination ($n = 3039$; 1512 men, 1527 women). All men and women with missing data on any of the considered risk factors were excluded ($n = 189$). Finally, 2850 study participants (1414 men and 1436 women) aged 35–64 years formed the basis of this report.

Data collection

Baseline information on smoking habits, medication use, personal history of disease, and alcohol consumption were gathered by trained medical staff during a standardized interview. In addition, all participants underwent an extensive standardized medical examination. All measurement procedures have been described in detail elsewhere.[17] Body mass index (BMI) was calculated as weight in kilograms divided by height in square metres. Systolic and diastolic blood pressure was measured on the right arm in a sitting position using a Hawksley random-zero sphygmomanometer adhering to the WHO MONICA protocol and the recommendations of the American Heart Association.[17] Persons being aware of having hypertension, taking anti-hypertensive medication, and/or having blood pressure values $\geq$160/95 mmHg at baseline were defined as actual hypertensives. A regular smoker was defined as a subject who currently smoked at least one cigarette per day. Alcohol intake was classified into three categories: 0 g/day, 0.1–19.9 g/day, and $\geq$20 g/day for women; and 0 g/day, 0.1–39.9 g/day, and $\geq$40 g/day for men.

Clinical chemical measurements

A non-fasting venous blood sample was obtained from all study participants while sitting. Total serum cholesterol analyses were carried out with an auto-analyser using an enzymatic method (CHOD-PAP; Boehringer Mannheim, Mannheim, Germany). The coefficient of variation for repeatedly measured duplicates was 1.1%. HDL-cholesterol was also measured enzymatically after precipitation of the apoprotein B-containing lipoproteins with phosphotungstate/Mg^{2+} (Boehringer Mannheim, Germany).

ApoB and A-I were analysed by kinetic immunoturbidimetry on a Hitachi auto-analyser, model 705. Measurements of apoB and A-I were carried out on frozen plasma (-78°C). The method is described in more detail elsewhere.[18] Standardization was performed with commercially available material (Boehringer Mannheim, Germany). Measurement ranges were 250–5000 and 200–4000 mg/L for apoB and A-I, respectively. The intra-assay coefficients of variation (CV) for apoB were between 2.5 and 1.5%. The corresponding values for the inter-assay CV were between 5.7 and 3.2%. Similar CVs were found for apoA-I. Comparison with radial immunodiffusion (IMMUNO Co., Heidelberg, Germany) showed excellent agreement ($r = 0.95$). Regular internal and external quality control procedures were carried out according to the recommendations of the WHO centre for lipid standardization in Prague.[19]

Study endpoints

The combined endpoint used in this study was incident fatal or non-fatal acute MI, and sudden cardiac death. They were identified through the MONICA/KORA Augsburg coronary event registry, which covered the same population from which the survey participants had been sampled. According to the MONICA manual, the diagnosis of a major non-fatal MI event was based on symptoms, cardiac enzymes (creatinine kinase, aspartate aminotransferase, lactate dehydrogenase), and typical ECG changes. Deaths from cardiovascular causes were validated by autopsy reports, death certificates, medical records, and information from the last treating physician.[20–22] An event was considered as incident if it was the first during follow-up in a person without a history of heart attack in the baseline survey. The MONICA diagnostic categories included definite and possible non-fatal acute MI and fatal CHD (combining definite and possible fatal coronary events and unclassifiable deaths). Detailed descriptions of the definitions and applications of these diagnostic categories have been published.[22]

In 1998, vital status was assessed for all participants of the survey through population registries inside and outside the study area. Death certificates were obtained from the local health departments and were coded for the underlying cause of death using the WHO classification rules by a single trained person using the ninth revision of the International Classification of Diseases (ICD-9). The codes were 410–414 for coronary artery disease. For analyses, event time was computed as the time from baseline examination to the first coronary event. For subjects without event, censoring times were calculated according to the last date of follow-up or the date of death.

Statistical analysis

All analyses were performed separately for men and women. For continuous variables as a measure of variability, the standard deviation (SD) was provided. Event rates were calculated for different values of the baseline characteristics with the use of a person-years (PY) approach. For this analysis, the distributions' upper tertiles were used to group each lipid parameter in two

classes (lower/equal or higher than upper tertile). The interquartile range (IQR) was defined as the interval from the 25% quartile to the 75% quartile. To assess the impact of each lipid and apolipoprotein parameter on the risk of an incident coronary event, age-adjusted and multivariable adjusted Cox proportional hazards models were computed.[23] Relative risks associated with an increase of 1 SD in the concentration of each lipid and apolipoprotein parameter were calculated in terms of hazard ratios (HRs). The TC/HDL cholesterol ratio was logarithmically transformed before inclusion in analysis as it was not normally distributed. For the logarithmically transformed TC/HDL cholesterol ratio, a 1 SD increase in the transformed variable was considered. Variables investigated for possible confounding included age (years), BMI (kg/m^2), regular smoking (yes/no), alcohol intake (three categories), history of diabetes (yes/no), actual hypertension (yes/no). Receiver-operating characteristic (ROC) analyses were used to estimate the discriminating ability for a first coronary event on the basis of a follow-up time of 10 years for both the apoB/apoA-I ratio and the TC/HDL cholesterol ratio. To compare the areas under two ROC curves (AUC), the method by DeLong *et al.*[24] was used. The assumption of proportionality of hazards was assessed by fitting models stratified by risk factor categories, then plotting the log [−log(survival)] curves to check parallelism. No severe deviations from parallelism were evident. The assumption of linearity was assessed graphically by studying the smoothed martingal residuals from the null model plotted against the covariate variables. Results are presented as HR together with their 95% confidence intervals (95% CI). Significance tests were two-tailed and *P*-values <0.05 were considered statistically significant. All analyses were performed using the Statistical Analysis System (Version 8.2, SAS Institute Inc., Cary, NC, USA).

Results

In total, 114 incident coronary events among men (53 fatal events, 61 non-fatal events) and 31 among women (18 fatal events, 13 non-fatal events) were registered in the 35 to 64-year-old study population between 1984 and 1998 (median follow-up period 13 years; IQR: 12.8–13.2).

Table 1 shows concentrations of lipids and apolipoproteins by age group and sex. ApoB values and total cholesterol values were related to age, whereas the values for apoA-I, the apoB/apoA-I ratio, and HDL-cholesterol varied less with age. The TC/HDL cholesterol ratio and non-HDL cholesterol were more closely related to age in women than in men. For all age groups, the mean concentration of apoB, the apoB/apoA-I ratio, and the TC/HDL cholesterol ratio were higher in men than in women. Total cholesterol and non-HDL cholesterol were also higher in men than in women in the lower two age groups, whereas in the highest age group it was higher in women than in men. Mean concentrations of apoA-I and HDL cholesterol were higher for women than for men.

Table 2 gives the number of incident coronary events, total follow-up years, and the unadjusted event rates

Table 1 Mean and SD of serum lipid and apolipoprotein levels measured at baseline in the study cohort of 1414 men and 1436 women by age group: MONICA Augsburg Survey 1984–85 with follow-up 1998 (MONICA/KORA cohort study S1)

	Age group (years)			
	All (35–64)	35–44	45–54	55–64
Men				
Total number of participants	($n = 1414$)	($n = 460$)	($n = 496$)	($n = 458$)
Age (years)	49.5 (8.4)	39.9 (3.0)	49.3 (3.1)	59.3 (2.9)
Total cholesterol (mg/dL)	241.9 (45.3)	235.7 (44.1)	245.2 (46.8)	244.4 (44.4)
HDL cholesterol (mg/dL)	50.8 (15.9)	50.3 (15.8)	50.9 (15.8)	51.1 (16.2)
Non-HDL cholesterol (mg/dL)	191.1 (48.2)	185.4 (47.1)	194.3 (49.1)	193.3 (47.9)
TC/HDL ratio[a]	4.9 (1.42)	4.8 (1.44)	4.9 (1.43)	4.9 (1.42)
ApoB (mg/dL)	89.5 (21.0)	86.8 (21.1)	90.5 (20.2)	91.2 (21.4)
ApoA-I (mg/dL)	136.3 (22.0)	135.0 (22.6)	137.6 (21.8)	136.3 (21.4)
ApoB/ApoA-I ratio	0.7 (0.20)	0.7 (0.21)	0.7 (0.19)	0.7 (0.21)
Number of coronary events	114	13	35	66
Women				
Total number of participants	($n = 1436$)	($n = 491$)	($n = 479$)	($n = 466$)
Age (years)	49.4 (8.6)	39.9 (3.0)	49.0 (2.9)	59.7 (2.9)
Total cholesterol (mg/dL)	237.0 (46.6)	214.7 (36.0)	236.1 (43.3)	261.5 (47.9)
HDL cholesterol (mg/dL)	63.5 (17.3)	65.3 (16.7)	63.4 (18.0)	61.7 (16.9)
Non-HDL cholesterol (mg/dL)	173.5 (48.0)	149.3 (36.5)	172.6 (44.8)	199.8 (48.4)
TC/HDL ratio[a]	3.8 (1.38)	3.3 (1.32)	3.8 (1.37)	4.3 (1.37)
ApoB (mg/dL)	80.8 (21.0)	71.7 (17.2)	80.3 (19.4)	90.9 (21.7)
ApoA-I (mg/dL)	153.5 (26.2)	152.7 (24.9)	153.8 (28.5)	154.1 (25.0)
ApoB/ApoA-I ratio	0.5 (0.18)	0.5 (0.14)	0.5 (0.17)	0.6 (0.19)
Number of coronary events	31	2	7	22

[a]Antilog.

Table 2 Number of incident coronary events in men and women, total PY, and unadjusted event rates for different values of the baseline characteristics

Baseline characteristics	Cases	Total PY	Event rate per 10 000 PY
Men			
Age			
<50 years	25	9044	27.6
≥50 years	89	7822	113.8
BMI			
<25 kg/m^2	21	4054	51.8
25–29.9 kg/m^2	65	9551	68.1
≥30 kg/m^2	28	3261	85.9
History of diabetes			
No	101	16 350	61.8
Yes	13	516	251.9
Hypertension			
No	79	13 201	59.8
Yes	35	3665	95.5
Alcohol intake			
0 g/day	17	2156	78.8
0.1–39.9 g/day	42	7594	55.3
≥40 g/day	55	7116	77.3
Regular smoker			
No	54	11 653	46.3
Yes	60	5213	115.1
TC/HDL ratio[a]			
<5.66	54	11 432	47.2
≥5.66	60	5434	110.4
Total cholesterol[a]			
<258.5 mg/dL	55	11 425	48.1
≥258.5 mg/dL	59	5441	108.4
HDL cholesterol[a]			
<55.0 mg/dL	87	10 990	79.2
≥55.0 mg/dL	27	5876	45.9
ApoA-I[a]			
<142.9 mg/dL	84	11 247	74.7
≥142.9 mg/dL	30	5619	53.4
ApoB[a]			
<96.6 mg/dL	50	11 471	43.6
≥96.6 mg/dL	64	5395	118.6
ApoB/ApoA-I ratio[a]			
<0.74	54	11 381	47.4
≥0.74	60	5485	109.4
Non-HDL cholesterol[a]			
<209 mg/dL	52	11 414	45.6
≥209 mg/dL	62	5452	113.7
Women			
Age			
<50 years	6	9886	6.1
≥50 years	25	7934	31.5
BMI			
<25 kg/m^2	6	7695	7.8
25–29.9 kg/m^2	12	6542	18.3
≥30 kg/m^2	13	3583	36.3
History of diabetes			
No	27	17 376	15.5
Yes	4	444	90.1
Hypertension			
No	14	14 512	9.6
Yes	17	3308	51.4
Alcohol intake			
0 g/day	16	6973	22.9
0.1–19.9 g/day	11	6735	16.3
≥20 g/day	4	4112	9.7
Regular smoker			
No	26	15 256	17.0
Yes	5	2565	19.5
TC/HDL ratio[a]			
<4.22	10	12 020	8.3
≥4.22	21	5801	36.2
Total cholesterol[a]			
<252.7 mg/dL	10	12 022	8.3
≥252.7 mg/dL	21	5799	36.2
HDL cholesterol[a]			
<68.9 mg/dL	25	11 830	21.1
≥68.9 mg/dL	6	5991	10.0
ApoA-I[a]			
<162.0 mg/dL	22	11 889	18.5
≥162.0 mg/dL	9	5931	15.2
ApoB[a]			
<86.7 mg/dL	9	12 014	7.5
≥86.7 mg/dL	22	5807	37.9
ApoB/ApoA-I ratio[a]			
<0.59	10	12 124	8.2
≥0.59	21	5697	36.9
Non-HDL cholesterol[a]			
<189.6 mg/dL	10	12 045	8.3
≥189.6 mg/dL	21	5776	36.4

[a]Each lipid parameter was categorized into two classes: lower/equal or higher than upper tertile.

per 10 000 PY for different values of the baseline characteristics. For all risk factors, incidence of a coronary event was higher in men than in women. The highest event rates were found in men and women with a history of diabetes (251.9 and 90.1 per 10 000 PY, respectively). In men, the event rate was more than twice as high for regular smokers than for casual and non-smokers, respectively. Other factors associated with incident coronary events in men and women were age, a history of hypertension, and BMI. Furthermore, the risk of an incident coronary event increased with increasing levels of total cholesterol, TC/HDL cholesterol ratio, non-HDL cholesterol, apoB, and apoB/apoA-I ratio, while an inverse association was seen for increasing concentrations of HDL-cholesterol and apoA-I in both sexes. In men, the event rate was 118.6/10 000 PY for apoB, 109.4/10 000 PY for the apoB/apoA-I ratio, and 110.4/10 000 PY for the TC/HDL ratio in the highest tertile compared with the first and second tertile; the corresponding values for women were 37.9/10 000 PY, 36.9/10 000 PY, and 36.2/10 000 PY, respectively.

The univariate risk ratios (adjusted for age) for each lipid and apolipoprotein factor are presented in *Table 3*. Increments of 1 SD (*Table 1*) of the TC/HDL cholesterol ratio and apoB were associated with significant increases in the

Table 3 Gender-specific, age-, and multivariable adjusted hazard ratios[a] for the risk of incident coronary events, MONICA Augsburg survey 1984–85 with follow-up 1998 (MONICA/KORA cohort study S1)

Variable	Age-adjusted HR (95% CI)	Multivariable-adjusted[b] HR (95% CI)
Men		
TC/HDL-ratio[c]	1.54 (1.29–1.85)	1.48 (1.22–1.78)
Total cholesterol	1.49 (1.27–1.76)	1.45 (1.22–1.73)
HDL-cholesterol	0.75 (0.61–0.94)	0.78 (0.62–0.98)
Non-HDL cholesterol	1.53 (1.32–1.79)	1.49 (1.26–1.75)
ApoA-I	0.89 (0.73–1.08)	0.91 (0.75–1.12)
ApoB	1.62 (1.36–1.93)	1.49 (1.25–1.78)
ApoB/ApoA-I ratio	1.50 (1.28–1.76)	1.42 (1.20–1.68)
Women		
TC/HDL-ratio[c]	1.96 (1.44–2.66)	1.69 (1.22–2.35)
Total cholesterol	1.62 (1.29–2.04)	1.71 (1.33–2.18)
HDL-cholesterol	0.61 (0.41–0.91)	0.74 (0.48–1.12)
Non-HDL cholesterol	1.74 (1.40–2.16)	1.79 (1.40–2.30)
ApoA-I	0.82 (0.55–1.21)	0.91 (0.62–1.32)
ApoB	1.74 (1.37–2.22)	1.73 (1.32–2.27)
ApoB/ApoA-I ratio	1.74 (1.31–2.31)	1.55 (1.15–2.11)

[a]Relative risk of an incident coronary event associated with an increase of 1 SD in the concentration of the respective variable.
[b]Adjusted for: diabetes, regular smoking, BMI (cont.), alcohol intake, actual hypertension, and age.
[c]TC/HDL ratio log-transformed.

risk of coronary events in men (HR = 1.54 and 1.62, respectively) and in women (HR = 1.96 and 1.74, respectively). Also, total cholesterol was a powerful predictor of coronary risk in both sexes (men, HR = 1.49; women, HR = 1.62). Furthermore, the apoB/apoA-I ratio and non-HDL cholesterol significantly increased the risk of coronary events in men (HR = 1.50 and 1.53, respectively) and women (HR 1.74 for both). Higher levels of HDL-cholesterol were associated with a significant lower risk of coronary events in men (HR = 0.75) and in women (HR = 0.61). Elevated apoA-I levels were also associated with decreased risk of a coronary event in both sexes (men, HR = 0.89; women, HR = 0.82), but this did not reach statistical significance. Furthermore, proportional hazards models were applied to find out whether the associations between concentrations of specific lipids and apolipoproteins and the risk of coronary events were modified by controlling for confounders (*Table 3*). Multivariable adjustment did not substantially attenuate the relationship between lipid or apolipoprotein concentrations and incidence of a coronary event. Only HDL-cholesterol, which showed a strong negative association with coronary events in univariate analysis, lost significance after multivariable adjustment in women.

When data were analysed by the ROC technique, assuming a follow-up time of 10 years, the apoB/apoA-I ratio showed an almost identical sensitivity and specificity to that of the TC/HDL cholesterol ratio in men and women (*Figure 1*). In men, the calculated AUC was 0.65 for the apoB/apoA-I ratio and 0.64 for TC/HDL cholesterol ratio, which was not statistically significantly different ($P = 0.31$). In women, the ability of the model based on the apoB/apoA-I ratio (AUC 0.74) to discriminate events from non-events was also virtually identical to that of the model based on the TC/HDL cholesterol ratio (AUC 0.76; $P = 0.33$).

Discussion

This large population-based study confirmed associations of total cholesterol, non-HDL cholesterol, and the TC/HDL cholesterol ratio with increased risk of coronary events in middle-aged men and women. The findings also provided support for a protective role of HDL-cholesterol in the manifestation of CHD. Furthermore, the present study showed a strong association between apoB and the apoB/apoA-I ratio and incident coronary events in both sexes even after adjustment for the conventional risk factors. However, a significant relationship between apoA-I and incident coronary events was not found in men or women. In both sexes, the predictive ability of the apoB/apoA-I ratio for incident coronary events within a follow-up period of 10 years was virtually identical to that of the TC/HDL cholesterol ratio.

In contrast to our data, in the Physicians' Health study[15] apoB levels were found not to predict future MIs after conventional risk factors and the ratio of TC/HDL cholesterol were considered. The Reykjavik study[14] and the Atherosclerosis Risk in Communities (ARIC) study[25] found apoB strongly predictive for CHD in univariate but not in multivariate analysis. In accordance with the present findings, the Québec study[13] strongly supported the importance of apoB as a risk factor for CHD in 45- to 76-year-old men followed up for 5 years. A further prospective study in 2508 UK men aged 50–61 years followed up for 6 years found that apoB was a better predictor of risk than total or LDL-cholesterol and that the ratio of apoB/apoA-I was associated with the strongest effect on risk.[26] Recently, results from the AMORIS study,[16] a large prospective study in Swedish men and women, followed up for an average of 5.5 years, showed that the concentration of apoB was superior to LDL-cholesterol in all direct comparisons. In contrast to the present study, in which the predictive power of the apoB/apoA-I ratio was similar to that of the TC/HDL ratio, in the AMORIS study, the apoB/apoA-I ratio was a better predictor of cardiovascular risk than any cholesterol ratio in both men and women. Also, in the Air Force/Texas Coronary Atherosclerosis Prevention study (AFCAPS/TexCAPS),[27] a primary prevention trial, baseline apoB, LDL-cholesterol, HDL-cholesterol, and on-treatment apoB and the apoB/apoA-I ratio were the best predictors of risk. Thus, the majority of prospective studies indicates that apoB is superior, or at least equal, to the usual lipid measurements to predict risk of CHD. Moreover, some prospective studies observed that the ratio of apoB/apoA-I was superior to TC/HDL cholesterol as an overall index of risk.

Several studies suggested that apoA-I may provide more information than HDL-cholesterol in the assessment of

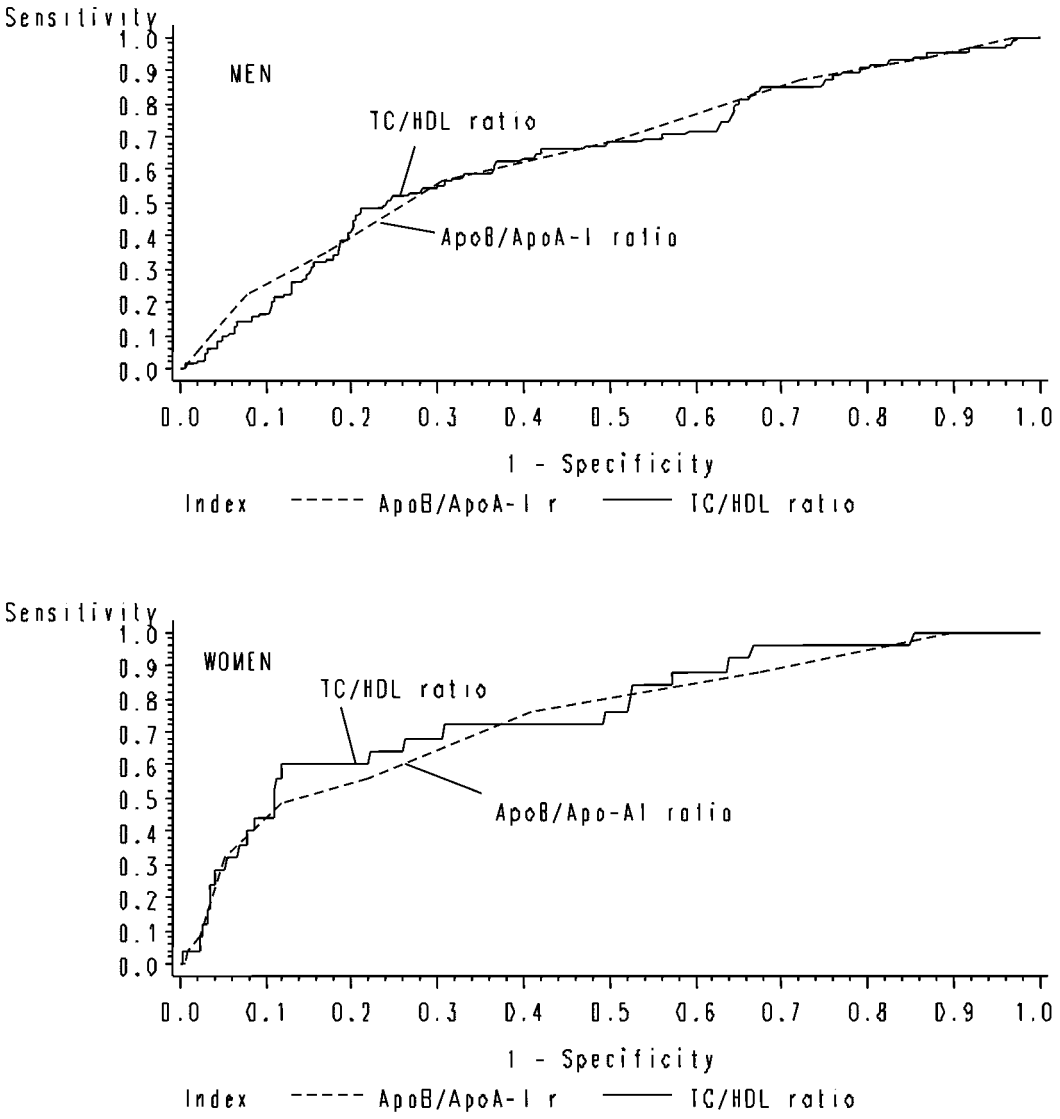

Figure 1 ROC curves for the apoB/apoA-I ratio and the TC/HDL cholesterol ratio in men and women on the basis of a follow-up time of 10 years. MONICA Augsburg survey 1984–85 with follow-up 1998 (MONICA/KORA cohort Study S1).

CHD.[10,11,28] In the AMORIS study,[16] apoA-I was an important risk factor for fatal MI, and retained its strong predictive power even when added to a model including total cholesterol and triglycerides in men. On the contrary, in the present study, a negative association with the incidence of a coronary event was found for apoA-I that did not reach statistical significance in age-adjusted analysis. In the ARIC study apoA-I was strongly predictive when considered alone but did not contribute to risk prediction at all when considered together with LDL, HDL, and triglycerides.[25] The Physicians' Health study[15] found that apoA-I did not add significantly to risk prediction in a multivariate model that included the TC/HDL cholesterol ratio. Also, the Quebec study[13] and the Northwick Park Heart study[26] found no statistically significant association between apoA-I and CHD risk in multivariable analysis. These results do not, in general, support the notion that apoA-I measurements may provide more information than HDL-cholesterol levels in the assessment of CHD. One reason for the lack of statistical significance might be that the present study and several others are smaller than AMORIS,[13,26] in which >175 000 study participants were included.[16] Thus, such smaller studies might not have the power to show a moderate protective effect of apoA-I.

In the present study, the predictive ability of non-HDL was almost identical to that of apoB in both sexes. Due to the good correlation between non-HDL cholesterol and apoB, measurement of non-HDL cholesterol has been argued to be comparable to the measurement of apoB.[29] However, studies have shown that non-HDL is not an acceptable clinical surrogate for apoB.[27,30] In the AFCAPS/TexCAPS study,[27] on-treatment concentration of apoB was superior to non-HDL cholesterol in predicting vascular events. Furthermore, the Quebec Cardiovascular study found that apoB and the various cholesterol indices are complementary rather than

competitive indices of atherosclerotic risk suggesting that measurement of apoB should be part of a standard lipoprotein assessment for CHD risk.[30] At the moment, in routine clinical practice, non-HDL cholesterol is more readily available than the measurement of apolipoproteins. However, meanwhile apolipoproteins can be accurately measured by commercially available autoanalysers in a standardized manner.[31,32]

The MONICA/KORA Augsburg Cohort study has a number of strengths that need to be mentioned. It comprises a large number of subjects drawn from the general population, and covers a median follow-up of 13 years. Furthermore, in contrast to most other prospective studies of this kind, we were able to examine the value of apoB and A-I in the prediction of a coronary event in both sexes within the same study population. In addition, the availability of a number of risk factors and clinical characteristics enabled us to adjust for multiple confounding variables. Because the MONICA/KORA MI registry in Augsburg is well established, we should have identified all incident events that occurred in the cohort.

However, several limitations of this study also need to be considered. Lipid and apolipoprotein levels were measured only once at baseline, so we were unable to account for intra-individual variability in the present study. The absolute values of apoB were lower than values obtained by IFCC/WHO internationally standardized methods.[31,32] Hence, although the conclusions of our study are valid, the absolute numbers cannot be directly compared with other reports. Moreover, because LDL cholesterol and triglyceride levels were not measured at baseline, these lipid measurements could not be included in the analysis. Furthermore, the borderline statistical significance in the present study could be due to the relatively low number of subjects with coronary events, particularly among women. For this reason, detailed separate analyses for fatal and non-fatal coronary events could not be carried out. Thus, the question of whether apoA-I may be more closely related to the risk of fatal coronary events in comparison with HDL cholesterol could not be clarified in the present study.

Finally, because the study was limited to subjects of German nationality between 35 and 64 years of age, caution should be used in generalizing these results to other populations and other age groups. However, the findings from this cohort are in general agreement with those of several other prospective epidemiological studies.

In conclusion, apoB and the apoB/apoA-I ratio were excellent discriminating risk factors for coronary events among men and women aged 35–64 years in this population-based cohort study. Therefore, apoB and the ratio of apoB/apoA-I are reliable measurements for inclusion in the CHD risk profile.

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