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Inflammation, the Metabolic Syndrome, and Risk of Coronary Heart Disease in Women and Men

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Abstract

Objective—This study examined whether inflammation adds to the prediction of coronary heart disease (CHD) beyond Metabolic Syndrome (MetS), and whether these associations differ between sexes.

Methods and Results—Among 30,111 women from the Nurses' Health Study and 16,695 men from the Health Professionals Follow-up Study without prior cardiovascular disease, 249 women and 266 men developed nonfatal myocardial infarction or fatal CHD during 8 and 6 years of follow-up, respectively. Controls were selected 2:1 within each cohort matched on age, smoking, and date of blood draw. Subjects with MetS had a significantly increased relative risk (RR) of CHD compared to individuals without MetS, and this RR was significantly higher in women (3.01; 95%-CI 1.98–4.57) than in men (1.62; 95%-CI 1.13–2.33; p interaction = 0.03). Adjustment for most inflammatory markers did not substantially attenuate the risk estimates, although the association was no longer significant in men after adjustment for CRP. Vice versa, associations of inflammatory markers with CHD risk among women were no longer significant after further adjustment for MetS. Among men, CRP and sICAM remained significant predictors of CHD independent of MetS.

Conclusions—MetS is a stronger predictor of CHD in women than in men. Most inflammatory markers did not add appreciable information beyond MetS to predict CHD; only CRP and sICAM remained independently predictive of CHD among men. The basis for these sex-based differences warrants further study.

Keywords

Metabolic syndrome; inflammation; epidemiology; cohort studies; coronary heart disease; risk factors

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Introduction

The metabolic syndrome (MetS) is a concept that encompasses metabolic abnormalities that tend to coexist to a greater degree than would be expected by chance alone, and which predispose individuals to an elevated risk of developing cardiovascular disease (CVD) and type 2 diabetes [1]. The National Cholesterol Education Program (NCEP) and the American Heart Association (AHA) as well as the International Diabetes Federation (IDF) have proposed algorithms to define MetS [2,3]. These definitions agree on the essential components of MetS, namely, glucose intolerance, obesity, hypertension, and dyslipidemia [2,3]. Inflammation – particularly elevated CRP – is also related to MetS and a risk factor for CVD [4–8]. However, in none of the current definitions is inflammation considered as a criterion to define MetS [2, 3,9]. Further, a recent study suggested that the associations of CRP with factors that currently define MetS are not causal [10]. Nevertheless, results from the West of Scotland Coronary Prevention Study (WOSCOPS), the Women's Health Study (WHS), and the Framingham Offspring Study suggest that CRP is a significant predictor of coronary heart disease (CHD) even after controlling for MetS [11–13]; however, controversy remains about the magnitude of information that CRP may add for CHD prediction beyond MetS. Further, only the Framingham report included men and women, thus allowing comparisons between both sexes [13]. The aim of our study was to examine whether inflammatory markers add to the prediction of CHD beyond MetS in nested case control studies from the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS); two well-described cohort studies of women and men. Further, we examined whether these associations differ between women and men.

Methods

Study Population

The NHS and the HPFS are prospective cohort investigations among 121,700 female US registered nurses aged 30–55 years at baseline in 1976 (NHS) and 51,529 US male health professionals, aged 40–75 years at baseline in 1986 (HPFS). Details on the methods to assess health and disease information, risk factors, biomarkers, and incident CHD in these cohorts have been published in detail elsewhere [6,14]. Between 1989 and 1990, a blood sample was requested from all participants in the NHS, and 32,826 women provided one. Similarly, between 1993 and 1995, a blood sample was provided as requested by 18,225 men in the HPFS. Participants who provided blood samples were similar to those who did not, albeit the men who provided samples were somewhat younger than those who did not. Among the 30,111 women in the NHS without cardiovascular disease (CVD) or cancer prior to 1990, we identified 249 women with incident nonfatal myocardial infarction or fatal CHD between date of blood drawing and June 1998. In the HPFS among the 16,695 men without CVD prior to 1994, we identified 266 men with similar incident CHD between date of blood draw around 1994 and return of the 2000 questionnaire. Using risk-set sampling [15], within each cohort controls were randomly selected 2:1 matched on age, smoking, and date of blood draw, from participants free of CVD at the time the case was diagnosed. Among the NHS an additional matching criterion was fasting status. Myocardial infarction was confirmed using World Health Organization's criteria and fatal CHD was confirmed by hospital records or on autopsy, or if CHD was listed as the cause of death on the death certificate, if it was the underlying and most plausible cause, and if evidence of previous CHD was available.

Measurement of biochemical variables

CRP and fibrinogen concentrations were determined using an immunoturbidimetric assay with reagents and calibrators from Denka Seiken (Niigata, Japan) and Kamiya Biomedical Co. (Seattle, WA, USA), respectively, with assay day-today variability between 1 and 2%. Soluble

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TNF receptor, interleukin-6, sICAM and sVCAM levels were measured by enzyme-linked immunosorbent assays from R&D Systems (Minneapolis, MN) with assay day-to-day variability between 3.5 and 9%. Inflammatory marker levels were largely unaffected by transport conditions and were reproducible within persons over time [16,17]. Total, HDL, and directly obtained LDL cholesterol, and triglycerides were measured using standard methods with reagents from Roche Diagnostics (Indianapolis, IN) and Genzyme (Cambridge, MA); all coefficients of variation were <6%. Study samples were sent to the laboratory for analysis in randomly ordered batches, and the laboratory was blinded to case-control status. The laboratory is certified by the Centers for Disease Control and Prevention/National Heart, Lung, and Blood Institute Lipid Standardization Program.

We excluded 97 women with missing information for TG, HDL-C, or HbA1c levels. Missing information for inflammatory markers among women were replaced by the median within this cohort (CRP, n = 15; sTNF-R, n = 7; IL-6, n = 33; sICAM, n = 4; sVCAM, n = 7; fibrinogen, n = 5). Results were similar when these women were excluded from the analysis.

Twenty-eight percent of women and 39% of men in our analysis provided non-fasting blood samples (time since last meal <8 hours). For TG levels, we subtracted the sex-specific geometric mean difference between non-fasting and fasting subjects from the individual levels of non-fasting subjects. Results were similar when we restricted our analysis to fasting subjects.

All participants gave written informed consent, and the study protocol was approved by the Institutional Review Board of the Brigham and Women's Hospital and the Harvard School of Public Health's Human Subjects Committee Review Board.

Definition of the metabolic syndrome (MetS)

The NCEP and the AHA defined MetS as having 3 or more of the following 5 abnormalities [2]: 1) abdominal obesity (waist circumference ≥88 cm in women or 102 cm in men); 2) elevated TG levels (≥150 mg/dL); 3) low HDL-C levels (<50 mg/dL in women and <40 mg/dL in men); 4) elevated blood pressure levels (≥130/≥85 mmHg); and 5) impaired fasting glucose levels (≥100 mg/dL). In the NHS and HPFS waist circumference, blood pressure, and blood glucose levels were not assessed at time of blood collection; therefore, we used a slightly modified definition of MetS, similar to the one used in the WHS [12]. Thus, we used a BMI of ≥28.0 kg/m^2 (NHS) and ≥27.4 kg/m^2 (HPFS) to define abdominal obesity; these values corresponded to the same percentile for BMI as a waist circumference of 88 cm (34.65 inches, NHS) and 102 cm (40.16 inches, HPFS), respectively, which were both self-reported in the years 1986 (NHS) and 1987 (HPFS). The validity of self-reported BMI and waist-circumference has been reported elsewhere [18]. Waist circumference was re-measured by the participants in NHS and HPFS and reported by questionnaire in 1996. The kappa coefficient for abdominal obesity defined based on these cutpoints and using BMI and waist circumference measured in 1996 was 0.53 (NHS) and 0.57 (HPFS), respectively, indicating moderate agreement between the two definitions. We defined abnormal glucose metabolism as history of diabetes, development of diabetes during follow-up, or HbA1c levels ≥6.5% at baseline. History of hypertension was used as a surrogate for elevated blood pressure levels.

Statistical analyses

We analyzed the two cohorts separately. Age-adjusted geometric mean inflammatory marker levels were compared between subjects with and those without MetS using linear regression with robust variance [19]. The relative risk (RR) of CHD in subjects with as compared to those without MetS was estimated using unconditional logistic regression, adjusting for age (5-year categories), smoking status (never, past, current), month of blood draw (5 categories), parental history of CHD before the age of 60 (yes/no), alcohol intake (nondrinker, 0.1 to 4.9 g/d, 5.0 to

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14.9 g/d, 15.0 to 29.9 g/d, ≥30.0 g/d, or missing), and physical activity (quintiles). In women we also adjusted for fasting status (yes/no) since this was a pre-defined matching factor, and for postmenopausal hormone therapy (yes/no). We repeated the main analysis using conditional logistic regression; because both analyses provided essentially the same results, we present unconditional logistic regression to include as many subjects as possible. With risk-set sampling, the odds ratio derived from logistic regression directly estimates the hazard ratio, and, thus, the RR [15]. To examine to what extent the inflammatory markers attenuate the association between MetS and CHD risk, inflammatory markers were categorized into quintiles based on the gender-specific distributions among controls and added individually and in combination as dummy variables to the regression model. Vice versa, we also calculated the RR of CHD in the highest versus lowest quintile for each inflammatory marker with and without further adjustment for MetS. To test for linear trend we used the median inflammatory marker levels in the control quintiles as a continuous variable. To test whether the association of MetS with risk of CHD were significantly different between men and women we combined the 2 cohorts, and, in addition to the other covariates, adjusted for sex, and included an interaction term (sex x MetS). Population attributable fractions were calculated from equations by Miettinen [20] and Bruzzi et al. [21], with 95%-CIs estimated by a variance formula proposed by Whittemore [22]. All p-values presented are two-tailed and p-values below 0.05 were considered statistically significant. Analyses were performed using SAS 9.1 (SAS Institute, Cary, NC).

Results

Mean age at baseline (time of blood draw) was 60.5 ± 6.5 years (range, 43.2–69.6 years) for women and 65.2 ± 8.3 years (46.6–80.8) for men. Women and men who developed CHD were more likely to have a higher number of metabolic abnormalities, and, consequently, were more likely to have MetS at baseline (Table 1). The prevalence of MetS among women was 40.6% in cases and 18.1% in controls ($p < 0.0001$), while among men it was 27.1% in cases and 17.9% in controls ($p = 0.003$). When individuals with diabetes were excluded the prevalence of MetS in women was 29.1% in cases and 14.4% in controls ($p < 0.0001$), and in men it was 22.8% in cases and 15.6% in controls ($p = 0.02$).

Individuals with MetS had significantly higher age-adjusted inflammatory marker levels than subjects without MetS, although the difference for sVCAM in men was not statistically significant (Table 2). These results were essentially unchanged when we excluded individuals with diabetes from our analyses.

Correlations among inflammatory markers have been reported previously for these cohorts [6]. Levels of sTNF-R1 and sTNF-R2 showed a high degree of correlation with each other. The correlation with and between the other inflammatory markers was moderate and ranged from 0.27 for the correlation between sTNF-R1 and CRP to 0.45 for the correlation between IL-6 and CRP.

The RR of CHD increased with increasing numbers of components of MetS in both sexes. Compared to women with no component of MetS the RRs were 1.95 (95%-CI 1.15–3.20) for women with 1 component; 3.38 (1.93–5.90) for those with 2; 4.75 (2.56–8.81) for those with 3; and 7.30 (3.74–14.25) for those with 4 or 5 components. Among men, the corresponding RRs were 1.40 (95%-CI 0.90–2.19); 2.67 (1.71–4.16); 2.33 (1.40–3.86); and 3.61 (1.84–7.09). Women with MetS had a RR of 3.01 for CHD (95%-CI 1.98–4.57) compared with women without MetS (Figure 1). This RR was significantly higher than for men (RR = 1.62; 95%-CI 1.13–2.33; p interaction = 0.03). The population fraction of CHD attributable to MetS was 27.1% (95%-CI 11.2%–40.2%) in women and 10.4% (95%-CI 2.3%–17.7%) in women. Further adjustment for most inflammatory markers only slightly attenuated the RR estimates

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for men and women (Figure 1), although the association was no longer statistically significant in men after adjustment for CRP. Adjusted for all inflammatory markers the RR for subjects with MetS as compared to those without was 2.74 (95%-CI 1.72–4.37) for women and 1.41 (95%-CI 0.96–2.07) for men (Figure 1, p sex interaction = 0.02). When individuals with diabetes were excluded from the analysis the RR of CHD was 2.40 (95%-CI 1.49–3.87) for women with MetS compared to those without and 1.56 (95%-CI 1.05–2.31) for men with compared to men without MetS (p interaction = 0.20).

Among women, in models that did not adjust for MetS (or its components), levels of CRP, soluble TNF receptors, and sICAM were significantly related to risk of CHD, whereas IL-6, sVCAM, and fibrinogen were not significant at the 5%-level (Table 3). After further adjustment for MetS none of these associations remained significant. Among men, only CRP and sICAM were significantly related to risk of CHD in models that did not adjust for MetS (Table 3). Further adjustment for MetS only slightly attenuated these associations; the RR in the highest compared to the lowest quintile after adjustment for MetS was 3.25 (95%-CI 1.83–5.78; p trend = 0.002) for CRP and 1.61 (95%-CI 1.01–2.57; p trend = 0.02) for sICAM. These results did not substantially change when individuals with diabetes were excluded from the analysis.

We next cross-classified subjects based on the absence or presence of MetS and on their plasma CRP levels (low, <1.0 mg/L; intermediate, 1.0–2.9 mg/L; and high,≥3.0 mg/L) and calculated RR for each category in comparison with the reference group of subjects without MetS and with low CRP levels (Figure 2). Among women, CRP categorization provided no additional information for CHD risk prediction. However, among men, CRP provided additional information for disease prediction among men without MetS, but not for men with MetS. The results were similar when we collapsed low and intermediate risk CRP levels. I.e., compared to women without MetS and CRP levels <3.0 mg/L the RRs were 1.28 (95%-CI 0.82–1.99) for women without MetS and CRP levels≥3.0 mg/L; 3.31 (1.75–6.26) for those with MetS and CRP <3.0 mg/L; and 3.31 (1.99–5.53) for those with MetS and CRP≥3.0 mg/L. The corresponding RRs among men were 1.72 (1.12–2.65); 1.81 (1.18–2.79); and 1.87 (1.04–3.39).

Discussion

In these two nested case control studies we found that women and men with MetS had significantly higher inflammatory marker levels and a significantly increased RR of CHD compared to subjects without MetS. The RR of CHD related to MetS was significantly higher in women than in men. The association between MetS and risk of CHD was independent of the levels of most inflammatory markers, although in men the association was no longer statistically significant after adjustment for CRP levels. Most of the inflammatory markers were not predictive of CHD risk when MetS status was taken into account; only CRP and sICAM remained independently predictive of CHD and this association was limited to men.

Differences in the strength of association between MetS and CVD may be caused by heterogeneity in outcomes, MetS definitions, and study populations. A recent meta-analysis that included 11 studies found that MetS was associated with a RR of 1.74 (1.43–2.12) for CVD [23]; however, the results were quite heterogeneous. Possible causes of the heterogeneity include the use of diverse cardiovascular endpoint definitions. Additionally, the different definitions of MetS include a broad range of disease entities. For example, some criteria used to define MetS include elevated fasting glucose levels (“pre-diabetes”) as well as manifest type 2 diabetes [2,3,24]. Thus, in the meta-analysis the RR in studies that excluded diabetics was 1.58, while in those that included diabetics it was 2.02 [23]. When we excluded subjects with diabetes at baseline from our analysis the RR of CHD was 2.40 in women and 1.56 in men. Differences across studies may also be related to the underlying study populations, particularly gender distribution. Only a limited number of studies have included both men and women,

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enabling a direct comparison between the sexes [13,25–28]. In agreement with our results, most of these studies found higher RRs associated with MetS in women than in men [13,25–27]. The reasons for this gender difference are unclear, but may be due, in part, to the stronger gradient in risk of CHD associated with low HDL-C and insulin resistance for women compared to men [29]. Another reason may be that men generally have a higher absolute risk of CHD than women.

Circulating inflammatory marker levels may predict cardiovascular events years in advance [4–6,30]. Observations from the NHS, the HPFS, and other studies suggest that among the inflammatory markers, CRP has been shown to be most consistently associated with coronary risk independent of traditional risk factors [6,31]. Inflammatory markers are also closely related to obesity, insulin resistance, diabetes, hypertension, and low HDL-C levels [6,32]. It is therefore not unexpected that we found significantly higher inflammatory marker levels in participants with MetS compared to those without. However, despite the close relationship of MetS with inflammation, adjustment for most inflammatory markers only modestly attenuated its association with CHD, suggesting that the effects of MetS on CHD are largely independent of inflammation. In contrast, only CRP and sICAM remained statistically significantly predictive of CHD risk after controlling for MetS, and this association was limited to men; among women, the predictive role of each of the inflammatory markers was eliminated after controlling for the presence or absence of MetS. While knowledge of inflammatory marker levels among diabetics may not influence the already aggressive medical management required for these patients we found similar results when these individuals were excluded. The reasons for the gender differences are unclear, but underline earlier speculations that mechanisms of insulin sensitivity rather than inflammation may contribute more to CHD risk in women than men [6]. Our results are in line with previous reports [11–13], suggesting that CRP predicts CVD events beyond MetS alone, but our results also suggest that the improvement in disease prediction may be small and limited to men. In the WHS, the risk of CVD was increased in women with MetS if they also had CRP levels ≥3.0 mg/L compared with <3.0 mg/L. In contrast, no such augmentation was observed among our cohorts in stratified analysis. Reasons for this dissimilarity may be related to differences in cardiovascular endpoints or in the degree of adjustment between the studies. Further, our stratified analysis may be limited by small numbers of cases within strata of MetS and CRP.

Because waist circumference measurements, blood pressure, and glucose levels were not available at baseline we used a modified definition of MetS which may limit the comparability with other studies. The prevalence of MetS among controls in our analysis using a modified NCEP definition was similar when compared to age-adjusted data published from NHANES for subjects ≥20 years using the NCEP definition (women, 23.4%; men, 24.0%) [33], but lower than what was reported for the age-categories of 50–59 years (prevalence between 30 and 35%) and for the age-categories of 60–69 years (between 40 and 45%) [33]. This is not unexpected given that our cohorts include health professionals. Further, our definition of MetS was based on identical criteria in the two cohorts and our primary purpose was to examine differences in the association of MetS with inflammatory markers and CHD risk between sexes. A similar definition has been used in a report from the WHS [12]. Any potential misclassification due to the use of a modified version of MetS in our study does not sufficiently explain why the strength of the association between MetS and CHD risk was different between men and women or why CRP was significantly related to CHD risk beyond MetS in men but not in women. Our cohorts do not represent random samples of the U.S. population, which may limit the generalizability of our results. However, the biological relationship between risk factors and cardiovascular outcomes found in this study should be similar to men and women in general. Previous studies have suggested that BMI may underestimate body fat and CHD risk in elderly men [34]. When we used a cut-off of 102 cm to define abdominal obesity based on waist circumference reported by the HPFS participants in 1996 (2 years past blood draw) in our

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study, the RR of CHD was 1.83 (95%-CI 1.27–2.64) in men with MetS compared to those without. We can therefore not rule out that the observed gender difference is due to the fact that BMI is less accurate to assess CHD risk in this population. We also can not completely rule out that the men and women may differ in their accuracy of describing self-reported risk factors. However, any potential inaccuracy should be minimal given that both cohorts include health professionals. Further, in a subsample of our cohorts we found correlation coefficients between self-reported weight and weight as measured by trained technicians of 0.97 for men and for women [18], indicating a similar accuracy for both sexes, at least for anthropometric factors. About one third of the members of our cohorts provided non-fasting blood samples, which may affect TG levels; however, we accounted for fasting status and found essentially the same results when we excluded non-fasting subjects. While the RR of CHD related to MetS was higher in women than in men it should be noted that the absolute risk of CHD in our cohorts was higher in men than in women. Also, it remains to be investigated whether the gender differences observed for CHD also apply to other cardiovascular endpoints. Finally, it should be noted that use of MetS for risk assessment and its designation as a syndrome has been questioned by some authors [35,36].

In conclusion, MetS was associated with elevated levels of inflammatory markers and was a stronger predictor of CHD in women than in men. Most inflammatory markers did not add appreciable information beyond MetS to predict CHD; only CRP and sICAM remained independently predictive of CHD and this association was limited to men. The basis for these sex-based differences warrants further study.

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Conflict of interest: Measurement of inflammatory markers was partly supported by a grant from Merck & Co., Inc. (West Point, PA). Dr. Manson is listed as a coinventor of a patent filed by Brigham and Women's Hospital related to inflammatory markers and diabetes mellitus. Dr. Girman is an employee of Merck & Co., Inc, which manufactures or is developing pharmaceutical products for the treatment of cardiovascular disease and diabetes.

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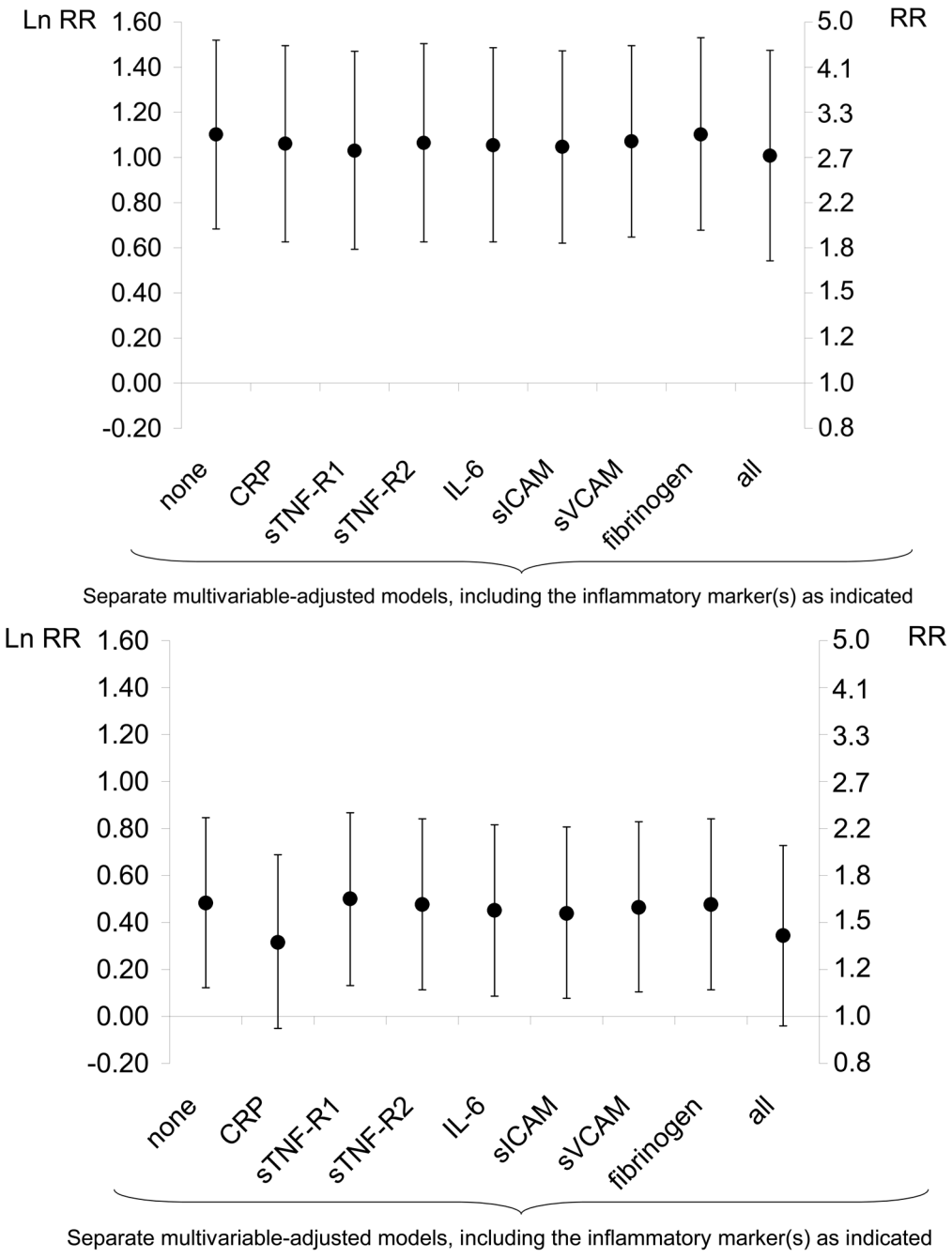

Figure 1.

Multivariable adjusted RR of CHD in women (Panel a) and men (Panel b) with MetS as compared to their counterparts without MetS (=reference group) with and without further adjustment for inflammatory markers. Dots indicate RRs; lines indicate 95%-confidence intervals. Each dot represents a separate model adjusted for age, smoking status, date of blood draw, parental history of CHD before age 60, alcohol consumption, and physical activity, with without further adjustment for the inflammatory marker(s) listed on the x-axis. In women additionally adjusted for fasting status, and HRT use. Note that RRs are plotted on a logarithmic scale.

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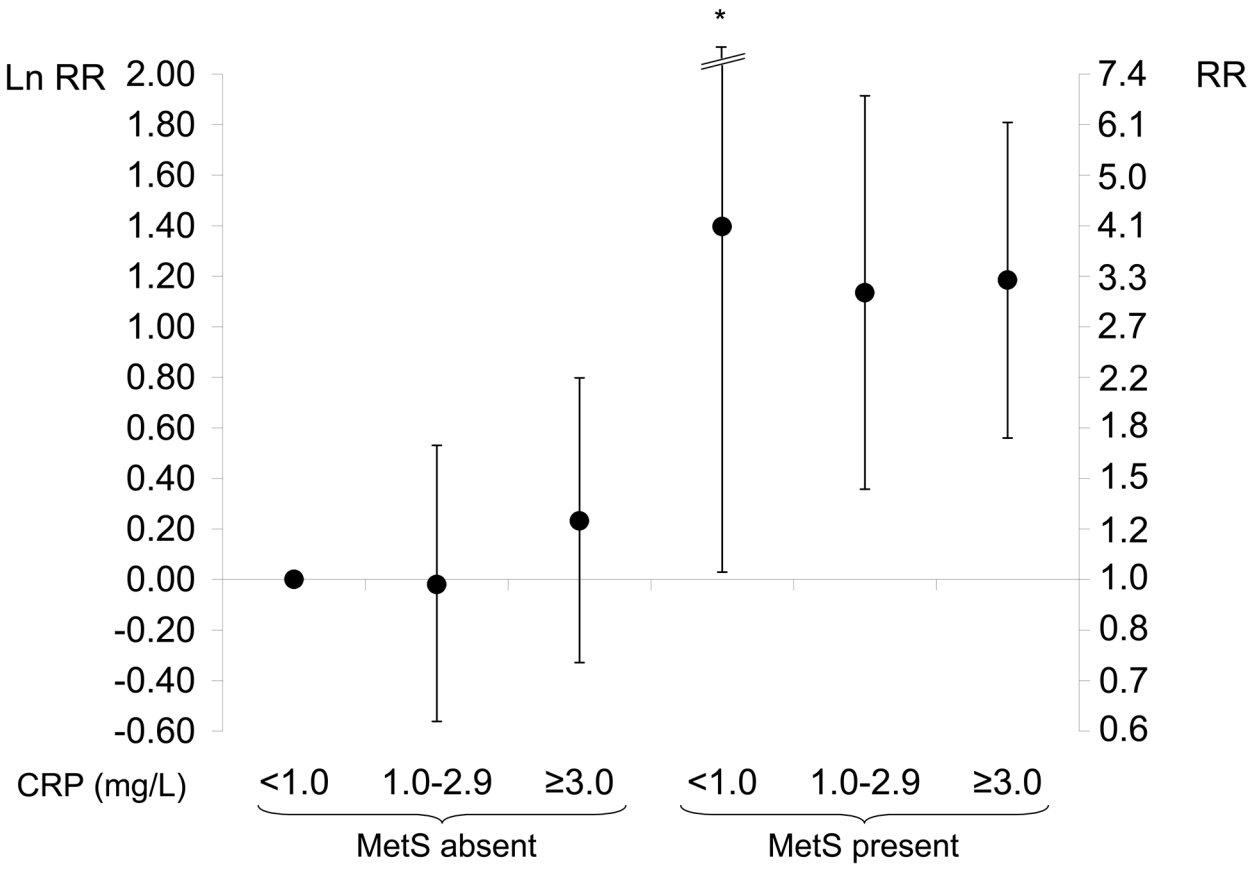

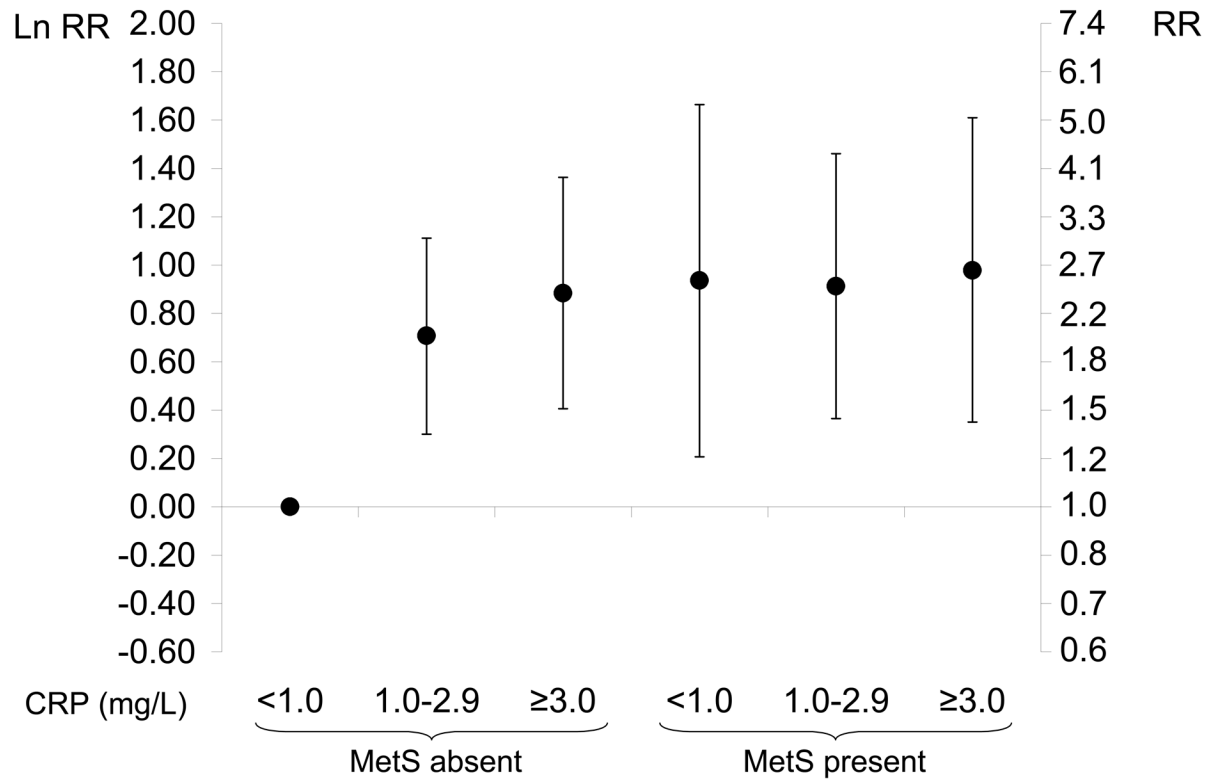

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Figure 2.

Multivariable adjusted RR of CHD in women (Panel a) and men (Panel b) according to categories of CRP and presence or absence of MetS. Dots indicate RR; lines indicate 95%-confidence intervals. Subjects without MetS and CRP levels <1 mg/L were used as the reference category. Models adjusted for age, smoking status, date of blood draw, parental history of CHD before age 60, alcohol consumption, and physical activity. In women additionally adjusted for fasting status, and HRT use. Note that RRs are plotted on a logarithmic scale.

*The upper boundary of the 95%-confidence interval for the RR of women with MetS and CRP levels <1 mg/L was 15.85.

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Table 1

Frequency of metabolic abnormalities and of the number of abnormalities defining the metabolic syndrome in participants with incident CHD (cases) and matched* event free controls among women and men

	Women			Men		
	Cases, %	Controls, %	p†	Cases, %	Controls, %	p†
Metabolic abnormality						
Abdominal obesity	43.4	31.8	0.004	30.5	26.1	0.20
High triglycerides	40.2	25.8	0.0002	47.7	32.5	<0.0001
Low HDL-C	51.1	30.4	<0.0001	47.0	35.0	0.001
High blood pressure	58.0	30.6	<0.0001	42.1	30.8	0.002
Abnormal glucose metabolism	28.8	10.9	<0.0001	15.0	7.5	0.0009
Number of metabolic abnormalities						
0	14.2	35.5	<0.0001	17.7	31.0	<0.0001
1	22.8	28.5		22.9	29.5	
2	22.4	17.9		32.3	21.6	
3	19.6	10.4		17.3	13.2	
4	10.1	4.4		6.0	3.8	
5	11.0	3.3		3.8	0.9	
> = 3	40.6	18.1	<0.0001	27.1	17.9	0.003

* matching criteria were age, smoking status, and date of blood drawing; in women additional matching criteria included fasting status

† P for difference between cases and controls (unadjusted), determined by the Chi-Square Test See text for definition of metabolic abnormalities

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Table 2

Age-adjusted inflammatory marker levels among controls with and without the metabolic syndrome for women and men*

Biomarker	Metabolic syndrome		
	No	Yes	P
	Women		
CRP (mg/L)	1.94 (1.73–2.17)	4.22 (3.48–5.11)	<0.001
sTNF-R1 (pg/mL)	1179 (1148–1212)	1462 (1382–1547)	<0.001
sTNF-R2 (pg/mL)	2305 (2246–2366)	2901 (2742–3068)	<0.001
IL-6 (pg/mL)	1.66 (1.55–1.77)	2.41 (2.07–2.81)	<0.001
sICAM (ng/mL)	260.9 (253.5–268.4)	285.1 (261.7–310.6)	0.05
sVCAM (ng/mL)	646.4 (631.7–661.4)	683.3 (654.2–713.7)	0.03
Fibrinogen (mg/dL)	329.6 (320.9–338.4)	365.9 (345.5–387.5)	0.001
	Men		
CRP (mg/L)	1.04 (0.93–1.16)	2.06 (1.68–2.53)	<0.001
sTNF-R1 (pg/mL)	1395 (1361–1430)	1605 (1511–1705)	<0.001
sTNF-R2 (pg/mL)	2782 (2716–2849)	3047 (2895–3206)	0.002
IL-6 (pg/mL)	1.69 (1.56–1.83)	2.54 (2.08–3.10)	<0.001
sICAM (ng/mL)	320.6 (313.3–328.1)	347.7 (328.9–367.7)	0.008
sVCAM (ng/mL)	1267.6 (1241.5–1294.1)	1320.4 (1262.1–1381.3)	0.11
Fibrinogen (mg/dL)	385.6 (379.1–392.3)	409.3 (392.8–426.5)	0.009

* Geometric means (95%-confidence intervals)

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Table 3

Multivariable adjusted relative risk of CHD in women and men in the highest versus lowest (=reference group) quintile of inflammatory markers with and without further adjustment for the metabolic syndrome.*

	Further adjustment for metabolic syndrome			
	No		Yes	
	RR (95%-CI)	P trend	RR (95%-CI)	P trend
	Women			
CRP	1.75 (0.98–3.10)	0.02	1.27 (0.70–2.32)	0.30
sTNF-R1	2.22 (1.23–4.00)	0.006	1.56 (0.84–2.89)	0.19
sTNF-R2	2.31 (1.22–4.35)	0.04	1.52 (0.78–2.96)	0.59
IL-6	1.58 (0.89–2.78)	0.06	1.19 (0.66–2.15)	0.42
SICAM	1.84 (1.02–3.31)	0.02	1.58 (0.87–2.88)	0.09
SVCAM	1.37 (0.79–2.39)	0.09	1.21 (0.68–2.13)	0.22
Fibrinogen	1.27 (0.72–2.22)	0.28	1.01 (0.57–1.81)	0.74
	Men			
CRP	3.54 (2.01–6.24)	<0.001	3.25 (1.83–5.78)	0.002
sTNF-R1	1.00 (0.59–1.69)	0.98	0.90 (0.53–1.53)	0.68
sTNF-R2	1.05 (0.63–1.74)	0.49	0.99 (0.59–1.65)	0.66
IL-6	1.50 (0.91–2.48)	0.09	1.44 (0.87–2.39)	0.12
SICAM	1.67 (1.05–2.66)	0.01	1.61 (1.01–2.57)	0.02
SVCAM	1.59 (0.98–2.60)	0.07	1.54 (0.94–2.52)	0.11
Fibrinogen	1.42 (0.85–2.37)	0.08	1.41 (0.84–2.35)	0.09

*Each line represents a separate model adjusted for age, smoking status, date of blood draw, parental history of CHD before age 60, alcohol consumption, and physical activity with and without further adjustment for the metabolic syndrome. In women additionally adjusted for fasting status, and HRT use.