ORIGINAL RESEARCH

C-Reactive Protein Identifies Low-Risk Metabolically Healthy Obese Persons: The European Prospective Investigation of Cancer–Norfolk Prospective Population Study

Diederik F. van Wijk, MD, PhD; S. Matthijs Boekholdt, MD, PhD; Benoit J. Arsenault, PhD; Sara Ahmadi-Abhari, MD, PhD; Nicholas J. Wareham, MBBS, PhD; Erik S. G. Stroes, MD, PhD; Kay-Tee Khaw, MBBChir

***Background*—**Conflicting data exist about the cardiovascular risk of metabolically healthy obese persons. The prognostic value of C-reactive protein (CRP) in this intriguing group is unknown. We assessed the association between CRP levels and the risk of coronary heart disease (CHD) in metabolically healthy persons with abdominal obesity.

***Methods and Results*—**In the European Prospective Investigation of Cancer–Norfolk prospective cohort, CRP levels and information on metabolic syndrome criteria were available for 7279 participants, of whom 825 (11%) developed CHD during a follow-up period of 10.9±1.8 years. There was a trend toward a higher multivariable-adjusted hazard ratio for CHD in metabolically healthy obese participants with CRP levels >2 mg/L compared with <2 mg/L (hazard ratio 1.59, 95% CI 0.97–2.62, *P*=0.066). Metabolically unhealthy obese participants had significantly higher CHD risk compared with metabolically healthy obese participants with CRP levels <2 mg/L (hazard ratio 1.88, 95% CI 1.20–2.94, *P*=0.006). Most important, we found that the risk of CHD among metabolically healthy obese persons with CRP levels <2 mg/L was comparable to that of metabolically healthy nonobese persons (hazard ratio 0.91, 95% CI 0.60–1.39, *P*=0.674).

***Conclusions*—**Among metabolically healthy obese persons, low CRP levels were associated with a CHD risk comparable to that of metabolically healthy nonobese persons. CRP appears to be an easy and widely available method for identifying a low-risk subpopulation among metabolically healthy obese persons. **(*J Am Heart Assoc*. 2016;5:e002823 doi: 10.1161/JAHA.115.002823)**

Key Words: atherosclerosis • inflammation • metabolic syndrome • obesity • risk factor

C-reactive protein (CRP) is an acute-phase protein of the family of the pentraxins and is widely used in clinical settings to monitor chronic and acute inflammatory conditions.[1] The positive association between CRP levels and the risk of future coronary heart disease (CHD) has been studied extensively.[2,3] The metabolic syndrome (MS) represents a cluster of risk factors for cardiovascular disease and type 2 diabetes mellitus, which coexist more often than by chance alone. It is widely accepted that the spectrum of MS includes abdominal obesity, hypertension, hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), and glucose intolerance, although the exact cutoff values are debated.[4,5] Two large meta-analyses have shown that the presence of MS raises CHD risk ≈2-fold.[6,7] Experimental and observational evidence suggests that inflammation may play a central role in the pathogenesis of cardiovascular disease.[8] CRP is associated with all parameters of the MS[9] and has been acknowledged to be an independent but not causal[2,10] risk factor for incident CHD and to add prognostic value for CHD risk on top of the MS criteria.[3,9,11–14]

The presence of obesity-related metabolic disturbances varies widely among obese persons. Metabolically healthy obese persons are characterized by having excessive body fat while displaying a favorable metabolic profile characterized by high levels of insulin sensitivity; no hypertension; and a favorable lipid, inflammation, hormonal, liver enzyme, and

From the Departments of Vascular Medicine (D.F.v.W., E.S.G.S.) and Cardiology (S.M.B.), Academic Medical Center, Amsterdam, The Netherlands; Centre de recherche de l'Institut universitaire de cardiologie et de pneumologie de Québec, Québec, Canada (B.J.A.); Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, United Kingdom (S.A.-A.); Medical Research Council Epidemiology Unit, Cambridge, United Kingdom (N.J.W., K.-T.K.).

Correspondence to: Diederik F. van Wijk, MD PhD, Department of Vascular Medicine, Academic Medical Center and Department of Cardiology, Onze Lieve Vrouwe Gasthuis, University of Amsterdam, Amsterdam, The Netherlands. E-mail: dfvanwijk@gmail.com

Received February 10, 2016; accepted April 7, 2016.

immune profile.[15] Recent studies have indicated that this healthier metabolic profile may not translate into a lower risk for mortality,[16,17] whereas other studies suggested that this population might have cardiovascular risk comparable to metabolically healthy nonobese persons.[18,19] To the best of our knowledge, the role of CRP in the assessment of CHD risk has not been described previously in metabolically healthy obese persons. We set out to determine the associations between CRP levels and the risk of CHD in this group. We tested the following hypotheses: Metabolically healthy obese persons with low levels of CRP (1) have lower cardiovascular risk than metabolically unhealthy obese persons with elevated levels of CRP and (2) have comparable risk of cardiovascular events compared with metabolically healthy nonobese persons. We examined these hypotheses in the European Prospective Investigation of Cancer–Norfolk (EPIC-Norfolk) prospective population study.

Methods

Study Design

EPIC-Norfolk is a prospective population study of 25 639 male and female inhabitants of Norfolk, United Kingdom, aged 39 to 79 years. Briefly, EPIC-Norfolk is part of the 10-country collaborative EPIC study designed to investigate determinants of cancer. Additional data were obtained to enable assessment of determinants of other diseases such as CHD. At the baseline survey between 1993 and 1997, participants completed a detailed health and lifestyle questionnaire with additional data collection performed by trained nurses at a clinic visit. The study cohort was similar to UK population samples with regard to many characteristics including anthropometry, blood pressure, and lipids but with a lower proportion of smokers. Full details of the population were reported elsewhere.[20]

MS criteria were defined as described previously, with minor modifications.[4] Abdominal obesity, obese persons, and obesity were all defined as an elevated waist circumference ≥102 cm (≥40 in) in men and ≥89 cm (≥35 in) in women. Hypertension was defined as systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg, or use of antihypertensive medication.[2] Hypertriglyceridemia was defined as triglyceride levels ≥150 mg/dL (1.7 mmol/L), whereas low HDL-C was defined as HDL-C <40 mg/dL (1.03 mmol/L) in men or HDL-C <50 mg/dL (1.30 mmol/L) in women. Hyperglycemia was defined as glycated hemoglobin HbA1c ≥6% or being on antidiabetic medication at inclusion. Participants were considered metabolically healthy when no or 1 MS criterion was present. Metabolically unhealthy was defined as the presence of ≥2 MS criteria. Metabolically healthy abdominally obese persons were defined as having an elevated waist circumference ≥102 cm (≥40 in) in men and ≥89 cm (≥35 in) in women without the presence of any of the other MS criteria.

All participants were flagged for mortality at the UK Office of National Statistics, with vital status ascertained for the entire cohort. The death certificates were coded by trained nosologists according to the *International Classification of Diseases, 10th revision* (ICD-10). In addition, participants were identified using their unique National Health Service numbers through data linkage with the East Norfolk Health Authority (ENCORE) database, which identifies all hospital contacts throughout England and Wales for residents of Norfolk. Participants were identified as having a CHD event if the corresponding ICD-10 code (I20–I25) was recorded as the underlying cause of that hospitalization or mortality. The study complied with the Declaration of Helsinki. The Norwich District Health Authority ethics committee approved the study, and all participants gave signed informed consent.

Laboratory Measurements

Nonfasting blood samples were drawn into plain and citrate bottles. Blood samples were processed directly at the Department of Clinical Biochemistry, University of Cambridge, or stored at −80°C. Serum levels of total cholesterol, HDL-C, and triglycerides were measured in fresh samples with RA 1000 (Bayer Diagnostics). Low-density lipoprotein cholesterol levels were calculated using the Friedewald formula. Because of limited funding, HbA1c levels were measured for participants from 1995 only; this approximates a random subset of the cohort. HbA1c was measured on fresh EDTA blood samples using high-performance liquid chromatography (Diamat Automated Glycated Hemoglobin Analyzer; Bio-Rad Laboratories Ltd). When additional funding became available in 2010, serum concentrations of CRP were measured for all participants with available frozen baseline serum samples using a full-range, high-sensitivity assay on an Olympus AU640 clinical chemistry analyzer (Olympus UK Ltd).

Statistical Analysis

For the current analysis, study participants with missing data for CRP, waist circumference, lipids, blood pressure, HbA1c, or use of antihypertensive or antidiabetic medication were excluded. Summary data are presented as mean±SD for continuous variables with a normal distribution, as median and interquartile range (IQR) for continuous variables with a non-normal distribution, and as percentage (number) for categorical variables. Because triglycerides and CRP were not normally distributed, these parameters were log-transformed before analysis. A 2-sided *t* test was used to test differences between groups for continuous variables, and a chi-square

test was used for categorical variables. A Cox proportional hazards model was used to assess the association between CRP levels and CHD. Associations were expressed as hazard ratios (HRs) and corresponding 95% CIs per 1-SD increment in (log-transformed) CRP. Participants were censored at the time of the first occurrence of the cardiovascular event analyzed, the time of death, or the end of follow-up, which was March 31, 2008, whichever came first. Three Cox regression models were performed to investigate the relation of CHD event rates, CRP, and (1) metabolically healthy or unhealthy persons, (2) persons with or without abdominal obesity, or (3) metabolically healthy or unhealthy persons with or without abdominal obesity. All models were adjusted for sex and age or for sex, age, smoking status, the use of lipid-lowering medication at baseline, and low-density lipoprotein cholesterol. Subgroup analyses to test for a possible interaction between sex and CRP was performed by the inclusion of an interaction term in the multivariable corrected model. The proportional hazards assumption was met for each variable in the model applied. The predefined level of significance was set at 0.05. Analyses were performed using IBM SPSS statistics version 20 (IBM Corp).

Results

CRP Levels and the MS Criteria

A complete data set on CRP levels, abdominal obesity, hypertension, hypertriglyceridemia, HDL-C, and HbA1c was available for 7279 participants. Table 1 shows the baseline characteristics according to metabolic phenotype and CRP level for the study participants. The mean age was 58 years, and 57% of participants were women. During follow-up, 825 (11%) CHD events occurred. There was a positive association between CRP level and number of MS criteria. CRP levels for those with 0, 1, 2, 3, or ≥4 MS criteria were 0.8 mg/L (IQR 0.4–1.7 mg/L), 1.2 mg/L (IQR 0.6–2.4 mg/L), 1.5 mg/L (IQR 0.8–3.1 mg/L), 2.2 mg/L (IQR 1.2–4.3 mg/L), and

Table 1. Baseline Characteristics

	Metabolically Healthy			Metabolically Unhealthy				
	CRP <2 mg/L	CRP ≥2 mg/L	*P* Value*	CRP <2 mg/L	CRP ≥2 mg/L	*P* Value†	*P* Value‡	All
Participants, n (%)	2685 (37)	997 (14)	—	1791 (25)	1806 (25)	—	—	7279
Age, y	55.7±9.2	58.3±9.0	—	59.5±9.3	62.2±8.8	—	—	58.4±9.4
Women, n (%)	1872 (64)	842 (67)	<0.001	647 (42)	790 (51.3)	<0.001	<0.001	4151 (57)
Body mass index, kg/m^2	24.6±3.0	26.5±3.9	<0.001	26.7±3.3	28.6±4.4	<0.001	<0.001	26.2±3.9
Waist circumference, cm	82.6±10.9	87.0±11.6	<0.001	91.3±11.0	95.6±11.6	<0.001	<0.001	88.0±12.4
Current smoker, n (%)	293 (10)	175 (14)	<0.001	132 (9)	234 (15)	<0.001	0.333	834 (11)
Diabetes mellitus, n (%)	10 (0.3)	8 (0.6)	0.182	55 (3.6)	76 (4.9)	0.061	<0.001	149 (2.0)
Myocardial infarction at baseline, n (%)	29 (1.0)	22 (1.7)	0.040	68 (4.4)	104 (6.7)	<0.001	<0.001	223 (3.1)
Systolic blood pressure, mm Hg	128±16	132±18	<0.001	140±17	143±17	<0.001	<0.001	134±18
Diastolic blood pressure, mm Hg	79±10	81±11	<0.001	86±11	86±10	0.405	<0.001	82±11
Total cholesterol, mmol/L	5.88±1.01	5.99±1.05	0.002	6.32±1.15	6.39±1.18	0.138	<0.001	6.10 ±1.11
LDL-C, mmol/L	3.72±0.94	3.80±0.98	0.012	4.08±1.03	4.12±1.04	0.208	<0.001	3.90±1.00
HDL-C, mmol/L	1.63±0.40	1.61±0.40	0.141	1.23±0.35	1.21±0.34	0.086	<0.001	1.45±0.43
Triglycerides, mmol/L	1.1 (0.9–1.5)	1.2 (1.0–1.5)	<0.001	2.2 (1.8–2.7)	2.2 (1.8–2.8)	0.017	<0.001	1.5 (1.1–2.2)
HbA1c, %	5.09±0.51	5.18±0.55	<0.001	5.46±0.91	5.76±1.15	<0.001	<0.001	5.3±0.83
CRP, mg/L	0.7 (0.4–1.2)	3.6 (2.5–6.1)	<0.001	1.0 (0.6–1.4)	4.0 (2.8–6.6)	<0.001	<0.001	1.4 (0.7–3.0)
Use of lipid-lowering drugs at baseline, n (%)	5 (0)	3 (0)	0.646	55 (3.6)	64 (4.2)	0.402	<0.001	127 (2)
Hormone replacement therapy, n (%)	344 (11.7)	298 (23.6)	<0.001	78 (5.1)	181 (11.7)	<0.001	<0.001	904 (12.4)

Data are presented as mean±SD or number (percentage). Triglyceride and CRP are presented as median with the 25th to 75th percentiles. CRP indicates C-reactive protein; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

**P* value of comparison within metabolically healthy groups with different levels of CRP.

†*P* value of comparison within metabolically unhealthy groups with different levels of CRP.

‡*P* value for comparison between metabolically healthy and unhealthy groups independent of CRP level.

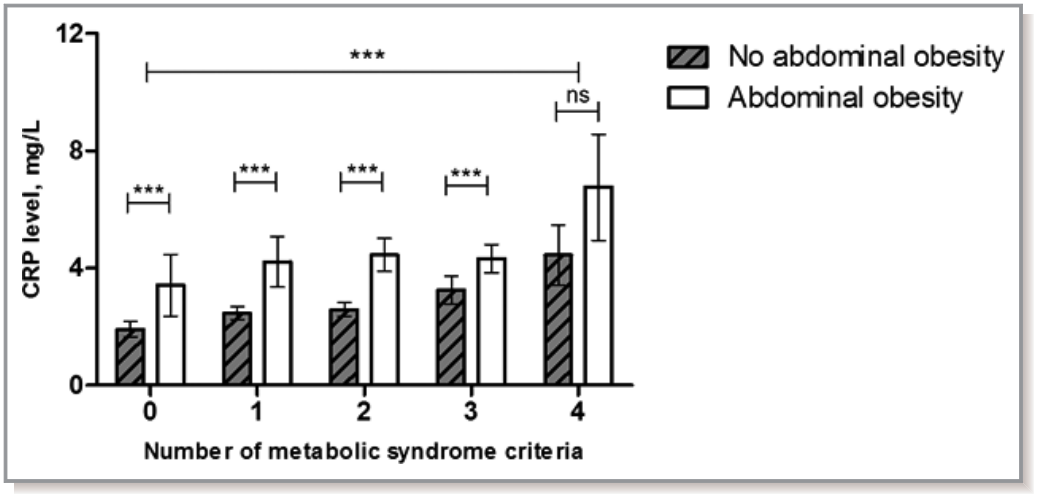

Figure 1. Distribution of CRP levels according to the number of MS criteria and the presence of abdominal obesity. Plots display the median and 25th and 75th percentiles of the CRP distribution. A Kruskal–Wallis nonparametric test demonstrated $P<0.01$ between number of MS criteria groups. A Mann–Whitney *U* test was used to test for significant differences in CRP level within the number of MS criteria groups. ***$P<0.01$. CRP indicates C-reactive protein; MS, metabolic syndrome; ns, not significant.

3.0 mg/L (IQR 1.6–5.7 mg/L), respectively (*P* for trend <0.001). Likewise, CRP levels were significantly higher in participants with versus without abdominal obesity independent of MS criteria (*P* for trend <0.001). Figure 1 displays the median and the 25th and 75th percentiles of the CRP distribution according to the number of MS criteria and the presence of abdominal obesity.

CRP and CHD Risk in Metabolically Healthy and Unhealthy Persons

HRs for CHD according to the presence or absence of metabolic health, abdominal obesity, and CRP level are shown in Table 2. Among metabolically unhealthy participants, those with CRP ≥2 mg/L had significantly higher CHD risk than those with CRP <2 mg/L (HR 1.37, 95% CI 1.16–1.63, *P*<0.001). Metabolically healthy participants with CRP levels <2 mg/L had a significantly lower risk than metabolically unhealthy participants with CRP levels <2 mg/L (HR 0.53, 95% CI 0.43–0.65, *P*<0.001). Compared with sex- and age-adjusted HRs, additional adjustment for smoking status, the use of lipid-lowering medication at baseline, and low-density lipoprotein cholesterol did not change these results importantly (HR 1.31, 95% CI 1.10–1.56, *P*=0.002, and HR 0.60, 95% CI 0.48–0.73, *P*<0.001, respectively).

CRP and CHD in Obese and Nonobese Persons

Among participants with abdominal obesity, those with CRP ≥2 mg/L had significantly higher CHD risk compared with those with a CRP level <2 mg/L (HR 1.45, 95% CI 1.14–1.85, *P*=0.002). Nonobese participants with CRP levels <2 mg/L had a significantly lower risk than those with abdominal obesity and CRP levels <2 mg/L (HR 0.73, 95% CI 0.58–0.92, *P*=0.008). Compared with sex- and age-adjusted HRs, additional adjustment for smoking status, lipid-lowering medication at baseline, and low-density lipoprotein cholesterol did not change the results importantly (HR 1.38, 95% CI 1.08–1.75, *P*=0.010, and HR 0.75, 95% CI 0.59–0.94; *P*=0.013, respectively).

CRP and CHD in Metabolically Healthy and Unhealthy Obese Persons

The risk of CHD for metabolically unhealthy obese participants with CRP <2 mg/L was significantly higher compared with metabolically healthy obese participants with CRP <2 mg/L (HR 1.88, 95% CI 1.20–2.94, *P*=0.006). The risk of CHD for metabolically healthy obese participants with CRP ≥2 mg/L was higher than that for metabolically healthy participants with CRP <2 mg/L (HR 1.59, 95% CI 0.97–2.62, *P*=0.066), although this trend did not reach statistical significance. Importantly, metabolically healthy participants without abdominal obesity had CHD risk comparable to metabolically healthy obese participants with CRP levels <2 mg/L (HR 0.91, 95% CI 0.60–1.39, *P*=0.674, for CRP <2 mg/L; HR 1.22, 0.78–1.91, *P*=0.387, for CRP >2 mg/L). Because sex is known to influence both CRP levels and CHD risk, we performed a subgroup analysis by sex to investigate a possible interaction between sex and CRP levels for risk of CHD. We did not find a statistical difference for the interaction of sex and CRP in the multivariable adjusted

Table 2. Hazard Ratios of Coronary Heart Disease Depending on Metabolic Phenotype or the Presence of Abdominal Obesity Stratified by C-Reactive Protein Levels

	CRP, mg/L	n (%)	Model 1	*P* Value	Model 2	*P* Value
Metabolically healthy	<2	2936 (40)	0.53 (0.43–0.65)	<0.001	0.60 (0.48–0.73)	<0.001
	≥2	1262 (17)	0.80 (0.64–1.01)	0.056	0.85 (0.68–1.01)	0.162
Metabolically unhealthy	<2	1540 (21)	1 (ref)	—	1 (ref)	—
	≥2	1541 (21)	1.37 (1.16–1.63)	<0.001	1.31 (1.10–1.56)	0.002
No abdominal obesity	<2	3730 (51)	0.73 (0.58–0.92)	0.008	0.75 (0.59–0.94)	0.013
	≥2	1697 (23)	1.10 (0.87–1.39)	0.420	1.03 (0.81–1.30)	0.811
Abdominal obesity	<2	746 (10)	1 (ref)	—	1 (ref)	—
	≥2	1106 (15)	1.45 (1.14–1.85)	0.002	1.38 (1.08–1.75)	0.010
Metabolically healthy without abdominal obesity	<2	2610 (36)	0.87 (0.57–1.33)	0.524	0.91 (0.60–1.39)	0.674
	≥2	925 (13)	1.24 (0.80–1.94)	0.336	1.22 (0.78–1.90)	0.387
Metabolically healthy abdominally obese	<2	326 (5)	1 (ref)	—	1 (ref)	—
	≥2	337 (5)	1.60 (0.98–2.63)	0.063	1.59 (0.97–2.62)	0.066
Metabolically unhealthy abdominally obese	<2	420 (6)	1.97 (1.26–3.09)	0.003	1.88 (1.20–2.94)	0.006
	≥2	769 (11)	2.53 (1.67–3.83)	<0.001	2.29 (1.51–3.47)	<0.001

Data presented as hazard ratios and corresponding 95% CIs. Model 1 is age and sex corrected. Model 2 is corrected for age, sex, smoking, the use of lipid-lowering medication at baseline, and low-density lipoprotein cholesterol. CRP indicates C-reactive protein.

model (*P*=0.511). Figure 2 displays CHD event rates according to the number of MS criteria and the presence of abdominal obesity in participants with either high or low CRP levels.

Discussion

The results of the present study indicated that metabolically healthy obese persons with low CRP levels had a trend toward

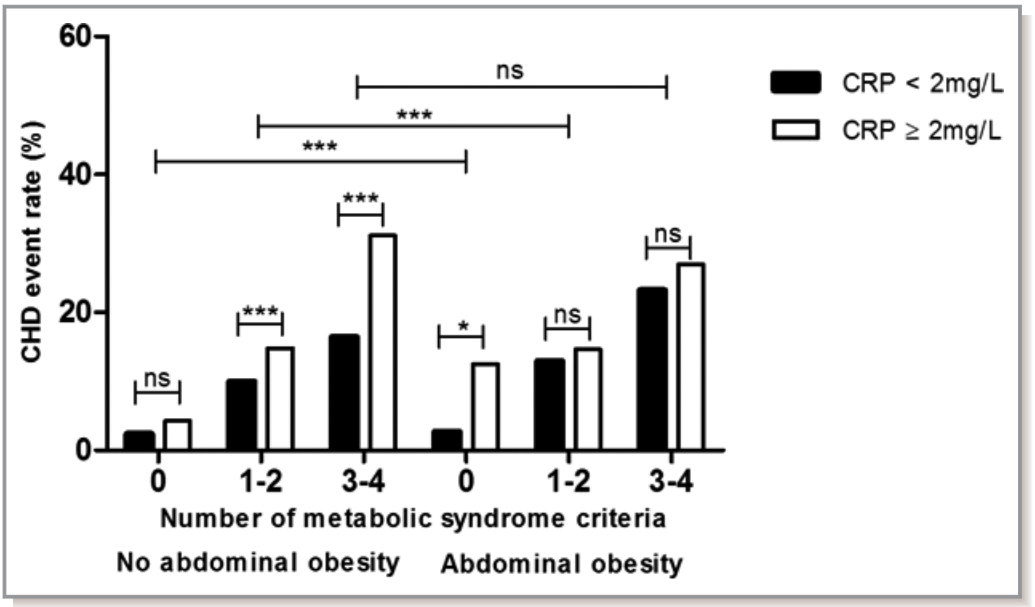

Figure 2. CHD event rates according to the number of MS criteria and the presence of abdominal obesity and the presence or absence of an elevated CRP level. A chi-square test was used to test for differences between event rates between and within the specified groups. To compare differences between the groups with no abdominal obesity and with abdominal obesity, all patients of each MS group were included in the analyses. **P*<0.05; ****P*<0.01. CHD indicates coronary heart disease; CRP, C-reactive protein; MS, metabolic syndrome; ns, not significant.

lower risk than metabolically healthy obese persons with elevated levels of CRP. More important, we observed that metabolically healthy obese persons with low CRP levels had a CHD risk similar to that of healthy nonobese persons. These data suggest that among metabolically healthy obese persons, low CRP levels are associated with low CHD risk.

Long-Term Risk for CHD

The positive association between CRP levels and the MS and between the MS and CHD have been studied extensively. Previous studies suggest that those with the MS or with elevated levels of CRP have an increased risk of CHD[9,21]; however, 2 large recently published meta-analyses assessing the associations of CRP concentration with risk of vascular outcomes did not include the MS in their subgroup analyses.[2,3] Our data indicate that metabolically unhealthy persons with elevated CRP levels have a significantly higher risk of future CHD compared with metabolically unhealthy persons with CRP levels <2 mg/dL. Ridker et al previously reported an age-adjusted HR of 2.3 (95% CI 1.6–3.3) for women with the MS if CRP levels <3 mg/L were present in contrast to the HR of 4.0 (95% CI 3.0–5.4) if CRP levels >3 mg/L were present.[9] Rutter et al similarly observed that CRP independently predicted CHD above the presence of the MS in the Framingham prospective cohort study.[12] We found similar associations for abdominally obese participants with elevated CRP levels showing an increased risk for CHD compared with abdominally obese participants with low CRP levels. Previous studies linking CRP levels to CHD were performed largely in populations with a lower prevalence of obesity than that of the current US population.[22–32] In the 2 largest published studies of CRP and CHD disease,[25,27] the mean body mass index (in kg/m^2) of participants ranged from 25 to 26, lower than the recently reported mean of 28.7 in US adults,[33] indicating the clinical need for data regarding CRP in obese populations. The Strong Heart Study examined the relationship between CRP levels and CHD in an obese population with a mean body mass index >30.[34] After multivariable adjustment for traditional risk factors, no significant association was observed between elevated CRP levels (>3 mg/L) and CHD events; however, subgroup analyses examining these relationships in obese and nonobese participants were not performed.[32] Similarly, Gupta et al reported that the association between CRP and atherosclerosis is diminished in obese persons aged 30 to 65 years.[35] The role of interleukin 6 was recently corroborated by 3 mendelian-based association studies.[36–38] Single-nucleotide polymorphisms associated with decreased interleukin 6 signaling were found to correlate with lower values of acute-phase reactants, such as CRP and fibrinogen, with a concomitant proportional reduction in cardiovascular risk. This lower predictive accuracy of CRP in obese participants may be affected by the close correlation between CRP and adiposity. Interleukin 6 is the principle cytokine that stimulates CRP release from the liver, and up to one-third of circulating interleukin 6 is released from adipose tissue.[39,40] Despite these data suggesting a weakened association in obese versus nonobese persons, our data showed that obese participants with elevated levels of CRP have a higher risk of future CHD than obese participants with CRP levels <2 mg/dL, suggesting that CRP adds prognostic information for the obese population, although the presence or absence of cardiometabolic risk factors may influence the predictive value of CRP in abdominally obese persons (Figure 2).

This study focused primarily on CRP and the risk of future cardiovascular events among participants recently characterized by Primeau et al: metabolically healthy obese persons. Despite having excessive body fat, these participants displayed a favorable metabolic profile characterized by high levels of insulin sensitivity; no hypertension; and a favorable lipid, inflammation, hormonal, liver enzyme, and immune profile.[15] Previous prospective studies provided mixed findings with regard to the prognosis of future CHD events in the metabolically healthy obese population. Three prospective studies observed that metabolically healthy obese persons have a risk of cardiovascular disease, mortality, and all-cause mortality similar to that of metabolically healthy nonobese persons.[18,41,42] In contrast, 2 other studies suggested that, compared with metabolically healthy nonobese persons, metabolically healthy obese persons have a higher risk of cardiovascular mortality and all-cause mortality.[16,17] More recently, Ortega et al showed that when accounting for fitness, cardiovascular risk was lower for metabolically healthy obese persons compared with metabolically unhealthy obese persons.[19] This study suggested that metabolically healthy obese persons might have decreased cardiovascular risk compared with their metabolically unhealthy peers because the metabolically healthy group is usually more physically fit. Our study showed that metabolically healthy obese participants with low CRP levels had a risk of future CHD similar to that of metabolically healthy nonobese participants as well as that of metabolically healthy nonobese participants with elevated CRP. These data suggest that CRP could help identify those metabolically healthy obese persons who are at low CHD risk.

Limitations and Strengths

When interpreting the results of our study, several aspects need to be taken into account. An important strength of this study is the relatively large number of CHD events occurring during follow-up (n=825). CRP levels and HRs for CHD were similar to those observed in previous publications.[3] The prevalence of metabolic risk criteria was in agreement with other large observational cohort studies, whereas the

prevalence of the metabolically healthy but obese phenotype was somewhat higher in our population compared with previous studies,[19] probably because we defined abdominal obesity by waist circumference, whereas other studies used other measures to determine obesity (eg, body mass index).[12] It must be noted that in view of the subgroups used in our analyses, differences in our population did not always reach our predefined significance level. This study was not designed and powered for the current analyses; therefore, the results should be considered as hypothesis generating and in need of confirmation in larger populations. In this prospective cohort study, changes in lipid-lowering therapy and diet were not recorded during follow-up. Statins and diet can decrease systemic CRP levels. The use of such medication or changes in diet could have altered CRP levels and the inherent cardiovascular risk.[43,44]

Conclusions

We confirmed a strong association between elevated CRP levels and an increased risk of CHD in abdominally obese or metabolically unhealthy persons. Importantly, our data indicated that among metabolically healthy obese persons, low CRP levels appeared to be associated with CHD risk comparable to that of healthy nonobese persons.

Acknowledgments

We thank the participants, general practitioners, and staff of the EPIC-Norfolk study. We are grateful to the laboratory teams of the Medical Research Council Epidemiology Unit for the coordination of the cohortwide biochemistry measurements.

Sources of Funding

EPIC-Norfolk is supported by program grants from the Medical Research Council UK and Cancer Research UK. The CRP measurements in the full cohort were supported by a grant from the Medical Research Council to the Medical Research Council Epidemiology Unit, Cambridge, United Kingdom (MRC G0701863). The funding sources had no role in the study design, the conduct of the analysis, or the decision to submit the manuscript for publication.

Disclosures

None.

References

1. Agrawal A, Singh PP, Bottazzi B, Garlanda C, Mantovani A. Pattern recognition by pentraxins. *Adv Exp Med Biol*. 2009;653:98–116.
2. Wensley F, Gao P, Burgess S, Kaptoge S, Di Angelantonio E, Shah T, Engert JC, Clarke R, Davey-Smith G, Nordestgaard BG, Saleheen D, Samani NJ, Sandhu M, Anand S, Pepys MB, Smeeth L, Whittaker J, Casas JP, Thompson SG, Hingorani AD, Danesh J. Association between C reactive protein and coronary heart disease: Mendelian randomisation analysis based on individual participant data. *BMJ*. 2011;342:d548.
3. Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, Danesh J. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet*. 2010;375:132–140.
4. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation*. 2004;109:433–438.
5. Lim HS, Patel JV, Lip GYH. Metabolic syndrome: a definition in progress. *Circulation*. 2004;110:e35; author reply e35.
6. Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, Montori VM. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol*. 2007;49:403–414.
7. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, Rinfret S, Schiffrin EL, Eisenberg MJ. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;56:1113–1132.
8. Rocha VZ, Libby P. Obesity, inflammation, and atherosclerosis. *Nat Rev Cardiol*. 2009;6:399–409.
9. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. *Circulation*. 2003;107:391–397.
10. Zacho J, Tybjaerg-Hansen A, Jensen JS, Grande P, Sillesen H, Nordestgaard BG. Genetically elevated C-reactive protein and ischemic vascular disease. *N Engl J Med*. 2008;359:1897–1908.
11. Aguilar D, Fisher MR, O'Connor CM, Dunne MW, Muhlestein JB, Yao L, Gupta S, Benner RJ, Cook TD, Edwards D, Pfeffer MA. Metabolic syndrome, C-reactive protein, and prognosis in patients with established coronary artery disease. *Am Heart J*. 2006;152:298–304.
12. Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB, Wilson PWF. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. *Circulation*. 2004;110:380–385.
13. Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly DSJ, Haffner SM, Isles C, Macfarlane PW, Packard CJ, Cobbe SM, Shepherd J. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation*. 2003;108:414–419.
14. Malik S, Wong N, Franklin S, Pio J. Cardiovascular disease in US patients with metabolic syndrome, diabetes, and elevated C-reactive protein. *Diabetes*. 2005;28:690–693.
15. Primeau V, Coderre L, Karelis AD, Brochu M, Lavoie M-E, Messier V, Sladek R, Rabasa-Lhoret R. Characterizing the profile of obese patients who are metabolically healthy. *Int J Obes (Lond)*. 2011;35:971–981.
16. Arnlöv J, Ingelsson E, Sundström J, Lind L. Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. *Circulation*. 2010;121:230–236.
17. Kuk JL, Ardern CI. Are metabolically normal but obese individuals at lower risk for all-cause mortality? *Diabetes Care*. 2009;32:2297–2299.
18. Meigs JB, Wilson PWF, Fox CS, Vasan RS, Nathan DM, Sullivan LM, D'Agostino RB. Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. *J Clin Endocrinol Metab*. 2006;91:2906–2912.
19. Ortega FB, Lee D-C, Katzmarzyk PT, Ruiz JR, Sui X, Church TS, Blair SN. The intriguing metabolically healthy but obese phenotype: cardiovascular prognosis and role of fitness. *Eur Heart J*. 2013;34:389–397.
20. Day N, Oakes S, Luben R, Khaw KT, Bingham S, Welch A, Wareham N. EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. *Br J Cancer*. 1999;80(suppl 1):95–103.
21. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med*. 1997;336:973–979.
22. Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation*. 1998;98:731–733.
23. Rost NS, Wolf PA, Kase CS, Kelly-Hayes M, Silbershatz H, Massaro JM, D'Agostino RB, Franzblau C, Wilson PW. Plasma concentration of C-reactive protein and risk of ischemic stroke and transient ischemic attack: the Framingham study. *Stroke*. 2001;32:2575–2579.

24. Mora S, Rifai N, Buring JE, Ridker PM. Additive value of immunoassay-measured fibrinogen and high-sensitivity C-reactive protein levels for predicting incident cardiovascular events. *Circulation*. 2006;114:381–387.
25. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med*. 2002;347:1557–1565.
26. Albert CM, Ma J, Rifai N, Stampfer MJ, Ridker PM. Prospective study of C-reactive protein, homocysteine, and plasma lipid levels as predictors of sudden cardiac death. *Circulation*. 2002;105:2595–2599.
27. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, Lowe GD, Pepys MB, Gudnason V. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med*. 2004;350:1387–1397.
28. Koenig W, Sund M, Fröhlich M, Fischer HG, Löwel H, Döring A, Hutchinson WL, Pepys MB. C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984. *Circulation*. 1999;99:237–242.
29. Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Multiple Risk Factor Intervention Trial. *Am J Epidemiol*. 1996;144:537–547.
30. Festa A, D'Agostino R, Williams K, Karter AJ, Mayer-Davis EJ, Tracy RP, Haffner SM. The relation of body fat mass and distribution to markers of chronic inflammation. *Int J Obes Relat Metab Disord*. 2001;25:1407–1415.
31. Pradhan AD, Manson JE, Rossouw JE, Siscovick DS, Mouton CP, Rifai N, Wallace RB, Jackson RD, Pettinger MB, Ridker PM. Inflammatory biomarkers, hormone replacement therapy, and incident coronary heart disease: prospective analysis from the Women's Health Initiative observational study. *JAMA*. 2002;288:980–987.
32. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999–2008. *JAMA*. 2010;303:235–241.
33. Walls HL, Stevenson CE, Mannan HR, Abdullah A, Reid CM, McNeil JJ, Peeters A. Comparing trends in BMI and waist circumference. *Obesity*. 2011;19:216–219.
34. Best LG, Zhang Y, Lee ET, Yeh J-L, Cowan L, Palmieri V, Roman M, Devereux RB, Fabsitz RR, Tracy RP, Robbins D, Davidson M, Ahmed A, Howard BV. C-reactive protein as a predictor of cardiovascular risk in a population with a high prevalence of diabetes: the Strong Heart Study. *Circulation*. 2005;112:1289–1295.
35. Gupta NK, de Lemos JA, Ayers CR, Abdullah SM, McGuire DK, Khera A. The relationship between C-reactive protein and atherosclerosis differs on the basis of body mass index: the Dallas Heart Study. *J Am Coll Cardiol*. 2012;60:1148–1155.
36. Niu W, Liu Y, Qi Y, Wu Z, Zhu D, Jin W. Association of interleukin-6 circulating levels with coronary artery disease: a meta-analysis implementing Mendelian randomization approach. *Int J Cardiol*. 2012;157:243–252.
37. Hingorani AD, Casas JP. The interleukin-6 receptor as a target for prevention of coronary heart disease: a Mendelian randomisation analysis. *Lancet*. 2012;379:1214–1224.
38. Sarwar N, Butterworth AS, Freitag DF, Gregson J, Willeit P, Gorman DN, Gao P, Saleheen D, Rendon A, Nelson CP, Braund PS, Hall AS, Chasman DI, Tybjærg-Hansen A, Chambers JC, Benjamin EJ, Franks PW, Clarke R, Wilde AAM, Trip MD, Steri M, Witteman JCM, Qi L, van der Schoot CE, de Faire U, Erdmann J, Stringham HM, Koenig W, Rader DJ, Melzer D, Reich D, Psaty BM, Kleber ME, Panagiotakos DB, Willeit J, Wennberg P, Woodward M, Adamovic S, Rimm EB, Meade TW, Gillum RF, Shaffer JA, Hofman A, Onat A, Sundström J, Wassertheil-Smoller S, Mellström D, Gallacher J, Cushman M, Tracy RP. Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. *Lancet*. 2012;379:1205–1213.
39. Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, Klein S, Coppack SW. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. *J Clin Endocrinol Metab*. 1997;82:4196–4200.
40. Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V. Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? *Atherosclerosis*. 2000;148:209–214.
41. Calori G, Lattuada G, Piemonti L, Garancini MP, Ragogna F, Villa M, Mannino S, Crosignani P, Bosi E, Luzi L, Ruotolo G, Perseghin G. Prevalence, metabolic features, and prognosis of metabolically healthy obese Italian individuals: the Cremona Study. *Diabetes Care*. 2011;34:210–215.
42. St-Pierre AC, Cantin B, Mauriège P, Bergeron J, Dagenais GR, Després J-P, Lamarche B. Insulin resistance syndrome, body mass index and the risk of ischemic heart disease. *CMAJ*. 2005;172:1301–1305.
43. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195–2207.
44. van Bussel BC, Henry RM, Ferreira I, van Greevenbroek MM, van der Kallen CJ, Twisk JW, Feskens EJ, Schalkwijk CG, Stehouwer CD. A healthy diet is associated with less endothelial dysfunction and less low-grade inflammation over a 7-year period in adults at risk of cardiovascular disease. *J Nutr*. 2015;145:532–540.