C-reactive protein as a predictor for incident diabetes mellitus among middle-aged men: results from the MONICA Augsburg cohort study, 1984-1998

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ORIGINAL INVESTIGATION

C-Reactive Protein as a Predictor for Incident Diabetes Mellitus Among Middle-aged Men

Results From the MONICA Augsburg Cohort Study, 1984-1998

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Background: Previous studies have suggested that low-grade systemic inflammation is involved in the pathogenesis of type 2 diabetes mellitus.

Objective: To investigate the association between C-reactive protein (CRP), the classic acute-phase protein, and incident type 2 diabetes mellitus among middle-aged men.

Methods: A total of 2052 initially nondiabetic men aged 45 to 74 years who participated in 1 of the 3 MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) Augsburg surveys between 1984 and 1995 were followed up for an average of 7.2 years. Incidence of diabetes was assessed by questionnaire mailed to participants in 1998. High-sensitive CRP was measured by an immunoradiometric assay.

Results: A total of 101 cases of incident diabetes occurred during the follow-up period. The age-standardized incidence rate was 6.9 per 1000 person-years. Men with CRP levels in the highest quartile (CRP ≥2.91 mg/L) had a 2.7 times higher risk of developing diabetes (95% confidence interval, 1.4-5.2) compared with men in the lowest quartile (CRP ≤0.67 mg/L) in a Cox proportional hazards model adjusted for age and survey. After further adjustment for body mass index, smoking, and systolic blood pressure, the observed association was significantly reduced and became nonsignificant.

Conclusions: Low-grade systemic inflammation is associated with an increased risk of type 2 diabetes mellitus in middle-aged men. Inflammation could be one mechanism by which known risk factors for diabetes mellitus, such as obesity, smoking, and hypertension, promote the development of diabetes mellitus.

C-REACTIVE PROTEIN (CRP), a sensitive marker of systemic inflammation, has been shown to be increased in patients with type 2 diabetes mellitus.[1,2] In addition, CRP levels are elevated in individuals with features of the metabolic syndrome[3-10] and with cardiovascular disease.[3,11] Although several prospective studies[12,13] have also consistently shown that CRP predicts myocardial infarction and other cardiovascular end points, little is known about the association between CRP and incident type 2 diabetes mellitus. Given the hypothesis that type 2 diabetes mellitus and atherosclerotic vascular disease may arise from a "common soil"[14,15] and that inflammation may be an important antecedent factor for both diseases,[16,17] we assumed that CRP, the classic acute-phase protein, might be related to incident diabetes mellitus. To further elucidate the mechanisms involved in the pathogenesis of type 2 diabetes, we examined the association between CRP and diabetes mellitus prospectively in a large cohort of men from the general population.

METHODS

STUDY POPULATION

The MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) Augsburg (Germany) project was part of the multinational World Health Organization MONICA project.[18] Three independent cross-sectional surveys were performed in Augsburg and the surrounding counties between 1984 and 1995. The study participants were 4022 men and women in 1984-1985 (age range, 25-64 years), 4940 in 1989-1990 (age range, 25-74 years), and 4856 in 1994-1995 (age range, 25-74 years). In 1998, vital status was assessed for all participants of the MONICA Augsburg surveys through population registries, and a questionnaire that assessed health status was sent to all subjects who were still alive.[19] Both base-

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line surveys and the follow-up study were approved by the local authorities. All participants gave written informed consent.

The present analysis is based on all men aged 45 to 74 years. Altogether, 3993 men aged 45 to 74 years had participated in at least 1 survey, of whom 481 had died between the baseline survey and follow-up. These subjects were excluded from the main analyses, because diagnosis of diabetes is usually underreported on death certificates in Germany. Furthermore, date of disease onset could only be estimated for these cases. Of the remaining 3512 subjects, 2396 (68%) had returned the questionnaire in 1998. Of these, 143 men with prevalent diabetes mellitus at baseline were excluded. For 12 subjects, no information about diabetes status at follow-up was available. Another 154 subjects had to be excluded because of missing CRP values, and for 25 subjects at least 1 of the covariables was missing. In addition, 10 incident cases of diabetes were excluded because these subjects reported a year of diagnosis in the follow-up questionnaire that lay before the year of the MONICA baseline examination, even though they had initially reported no diagnosis of diabetes at baseline. Thus, a total of 2052 initially nondiabetic men aged 45 to 74 years at baseline formed the basis for the analyses presented in this article.

DATA COLLECTION

Information concerning sociodemographic variables, smoking habits, physical activity level, personal and parental history of disease, and alcohol consumption was assessed by standardized personal interviews. Blood pressure, body height, body weight, and waist and hip circumference were determined by trained medical staff (mainly nurses). All measurement procedures have been described elsewhere in detail.[20,21] Body mass index (BMI) and waist-hip ratio (WHR) were calculated as weight in kilograms divided by the square of height in meters and waist circumference in centimeters divided by hip circumference in centimeters, respectively. Hypertension was defined as blood pressure of 160/95 mm Hg or higher and/or use of antihypertensive medication, given that subjects were aware that they had hypertension. Participants were classified as active during leisure time if they regularly participated in sports in summer and winter and if they were active for at least 1 hour per week in either season.

ASCERTAINMENT OF DIABETES AND DATE OF DIAGNOSIS

Prevalent and incident cases of diabetes were ascertained by self-report of subjects or the use of hypoglycemic medication. In the baseline questionnaire, subjects could give the following answers to the question "Do you have diabetes mellitus?": "yes," "no," or "I don't know." All subjects who answered "yes" were excluded. Those who answered "I don't know" (n=130) and were not taking any medication for diabetes were considered to be nondiabetic at baseline. They were excluded in the sensitivity analysis only. All subjects with prevalent diabetes at baseline reported that the disease had been diagnosed by a physician.

In the follow-up questionnaire, the question "Do you have diabetes mellitus?" could only be answered with "yes" or "no." A total of 95% of all subjects with incident diabetes reported that the disease had been diagnosed by a physician; in the remaining 5%, the answer to the respective question was missing. None of the participants denied a diagnosis by a physician. The calendar year of diagnosis was also ascertained by questionnaire. The midpoint of the reported year of diagnosis was used to calculate the follow-up time used in the proportional hazards models.

LABORATORY ANALYSES

A nonfasting venous blood sample was obtained from all participants while lying in a supine resting position. Serum CRP concentrations were measured using a high-sensitive immunoradiometric assay (range, 0.05-10 mg/L).[22] The coefficient of variation for repeated measurements was 12% for all ranges. Samples for measurement of CRP were stored at −80°C until analysis. Total serum cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) levels were measured by enzymatic methods (CHOD-PAP; Boehringer Mannheim, Mannheim, Germany). Low-density lipoprotein cholesterol (LDL-C) levels were measured with a precipitation test (QUANTOLIP-LDL; Immuno AG, Vienna, Austria) in the last 2 surveys only.

STATISTICAL METHODS

Incidence rates for diabetes mellitus were age standardized, using the population of the Federal Republic of Germany as of December 31, 1989.[23] Differences in demographic and clinical characteristics between subjects who developed diabetes during the follow-up period and those who remained free of the disease were analyzed using *t* tests for continuous variables and χ^2 tests for categorical variables. Differences in CRP levels by demographic and clinical characteristics were compared using analysis of variance. Since the distribution of CRP levels was highly skewed, CRP levels were log transformed and geometric mean concentrations were calculated.

Cox proportional hazards analysis was used to determine the independent association between CRP levels at baseline and incident type 2 diabetes. The CRP levels were categorized into quartiles based on the concentrations measured in all participants included in this analysis. Variables investigated for possible confounding included age, survey, BMI, smoking status (never smoker, former smoker, current smoker), education (<12 years of schooling, ≥12 years of schooling), leisure time physical activity level (active, not active), alcohol intake (0, >0 and <40, or ≥40 g/d), parental history of diabetes mellitus (negative, unknown, positive), history of myocardial infarction, history of angina, systolic and diastolic blood pressure, actual hypertension, TC level, HDL-C level, and the TC/HDL-C ratio. Since the number of events was small, we used a forward stepping procedure to keep the number of variables to a minimum. A 5% change of the hazard ratio (HR) for any quartile of CRP was used as the criteria for inclusion in the model. Age and survey were forced into the model from the beginning, and at each step the variable that changed the value of the HR most, when added to the other variables already in the model, was also included. Among blood pressure variables, we included only systolic blood pressure in the multivariable modeling process, since it had the strongest confounding effect in the age- and survey-adjusted model. For the same reason, the TC/HDL-C ratio was used. For all covariables used in continuous form in multivariable modeling, departures from linearity were initially checked by the use of categorical indicator variables. $P<.05$ was regarded as statistically significant. All analyses were performed with SAS statistical software (version 6.12; SAS Institute Inc, Cary, NC).

RESULTS

DIABETES INCIDENCE AND FOLLOW-UP TIME

During an average follow-up period of 7.2 years (range, 0.1-13.7 years), 101 new cases of diabetes were detected. The age-standardized incidence rate was 6.9 per 1000 person-years. The mean follow-up time (number of incident cases) was 12.6 years (n=40), 7.9 years (n=43), and 3.1 years (n=18) for participants in the first, second, and third surveys, respectively. Most incident cases (60%) were treated with oral antidiabetic tablets only, 6% were treated with insulin only, 6% were treated with tablets and insulin, and 25% were treated with diet only. For 3%, treatment was unknown.

STUDY POPULATION CHARACTERISTICS

Table 1 gives selected baseline demographic and clinical characteristics of the study participants by diabetes status at follow-up. The mean age of participants who developed diabetes was similar to participants who remained free of the disease. However, those who developed diabetes were heavier, had higher systolic and diastolic blood pressures, and were more likely to have hypertension, a history of angina, or a parental history of diabetes. They smoked more often, were less active during leisure time, were more likely to consume larger amounts of alcohol, and had higher TC and lower HDL-C concentrations compared with those who remained free of diabetes. The geometric mean CRP concentration at baseline was 43% higher in persons who developed diabetes compared with participants who did not. Concentrations ranged from 0.2 to 18.9 mg/L (median, 2.1 mg/L; interquartile range, 2.9 mg/L) in subjects with incident diabetes and from 0.1 to 74.5 mg/L (median, 1.4 mg/L; interquartile range, 2.2 mg/L) in subjects who remained free of diabetes. The prevalence of CRP values greater than 10 mg/L was 2.0% and 3.0% in subjects with and without diabetes, respectively.

ASSOCIATION BETWEEN CRP AND VARIOUS CARDIOVASCULAR RISK FACTORS

Logarithmically transformed CRP concentrations correlated significantly with a variety of other covariates. The correlation was strongest between log CRP and WHR (Pearson correlation coefficient $r=0.28$, $P<.001$) and BMI ($r=0.23$, $P<.001$). Slightly smaller correlations were observed for age ($r=0.17$, $P<.001$), HDL-C ($r=-0.15$, $P<.001$), TC/HDL-C ratio ($r=0.14$, $P<.001$), and systolic blood pressure ($r=0.11$, $P<.001$). For TC and LDL-C, the correlation coefficient was small, and diastolic blood pressure did not correlate at all with log CRP.

The association between CRP levels and several categorical covariates is given in **Table 2**. Participants with actual hypertension, a history of myocardial infarction, or angina had significantly higher geometric mean CRP concentrations compared with participants without these disorders. Smoking status was also strongly associated with CRP, with an almost 2-fold increased level in current smokers compared with never smokers.

ASSOCIATION BETWEEN CRP AND INCIDENT DIABETES MELLITUS

In Cox proportional hazards models, quartiles of CRP were significantly associated with incident diabetes mellitus, with an almost 3-fold increased risk in subjects in the top quartile of the CRP distribution compared with those in the bottom quartile (**Table 3**). After adjustment for age and survey, CRP levels remained an independent predictor of incident diabetes (models 2 and 3). However, further adjustment for BMI, smoking status, and systolic blood pressure considerably attenuated the observed HRs, and they were no longer significant (models 4 and 5). The inclusion of BMI as a covariable had a particularly strong impact on the HRs for quartiles of CRP, suggesting a strong pathogenetic interaction between CRP and obesity. The remaining potential confounders produced changes of less than 5% for any of the CRP quartile estimates when added to the previous model.

Table 1. Baseline Demographic and Clinical Characteristics of the Study Participants by Diabetes Status at Follow-up*

Characteristics	Men With Incident Diabetes During Follow-up (n = 101)	Men Without Incident Diabetes During Follow-up (n = 1951)	*P* Value†
Mean age, y	57.2	57.0	.77
Mean BMI	29.8	27.5	<.001
Mean WHR‡	0.96	0.94	.001
Mean SBP, mm Hg	144.1	137.2	<.001
Mean DBP, mm Hg	87.0	83.5	.003
Actual hypertension, %§	43.6	29.2	.002
History of MI, %	5.9	3.3	.16
History of angina, %	8.9	4.1	.02
Education <12 y, %	69.3	64.0	.28
Smoking status, %			
Current smoker	32.7	21.3	.02
Former smoker	43.6	46.2	
Never smoker	23.8	32.6	
Frequency of exercise, %			
Active	30.7	43.0	.02
Inactive	69.3	57.1	
Alcohol consumption, %			
0 g/d	14.9	14.7	.02
>0-39 g/d	40.6	53.6	
≥40 g/d	44.6	31.7	
Parental history of diabetes, %			
Positive	30.7	18.8	.003
Unknown	41.6	57.5	
Negative	27.7	23.7	
Mean TC, mmol/L	6.5	6.3	.048
Mean LDL-C, mmol/L‡	4.2	4.0	.14
Mean HDL-C, mmol/L	1.2	1.3	.02
Geometric mean of CRP, mg/L	2.0	1.4	<.001
CRP levels ≥2.9 mg/L, %	34.7	24.4	.02
Participants by survey, %‖			
Survey 1	39.6	24.6	.001¶
Survey 2	42.6	34.2	
Survey 3	17.8	41.2	

Abbreviations: BMI, body mass index (weight in kilograms divided by the square of height in meters); CRP, C-reactive protein; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; SBP, systolic blood pressure; TC, total cholesterol; WHR, waist-hip ratio (waist circumference in centimeters divided by hip circumference in centimeters).

SI conversion factors: To convert cholesterol from millimoles per liter to milligrams per deciliter, divide by 0.02586.

*N = 2052 men (age range, 45-74 years).

†*t* Test for continuous variables and χ^2 test for categorical variables.

‡Only measured in participants of survey 2 and 3 (diabetics: n = 61; nondiabetics: n = 1467).

§Defined as SBP of 160 mm Hg or higher and/or DBP of 95 mm Hg or higher and/or use of antihypertensive medication, given that subjects were aware that they had hypertension.

‖Survey 1 included only participants aged 45 to 64 years.

¶Differences in percentages between surveys are mainly caused by differing follow-up periods and differences in the age distribution.

Table 2. Geometric Mean Concentrations of Serum CRP and Antilog of SEs by Selected Categorical Covariates

Covariates	No. of Subjects (N = 2052)	Mean (Antilog) CRP, mg/L	SE (Antilog) CRP, mg/L	*P* Value*
Age, y				
45-54	874	1.22	1.04	<.001
55-64	746	1.45	1.04	
65-74	432	1.88	1.05	
BMI				
<25	407	0.99	1.05	<.001
25-30	1240	1.43	1.03	
≥30	405	2.04	1.05	
Actual hypertension†				
Yes	614	1.70	1.04	<.001
No	1438	1.32	1.03	
History of MI				
Yes	71	1.90	1.13	.02
No	1981	1.41	1.02	
History of angina				
Yes	89	1.81	1.12	.03
No	1963	1.41	1.02	
Education, y				
<12	1318	1.53	1.03	<.001
≥12	734	1.26	1.04	
Smoking status				
Current	448	2.15	1.05	<.001
Former	945	1.43	1.03	
Never	659	1.07	1.04	
Frequency of exercise				
Active	869	1.24	1.04	<.001
Inactive	1183	1.58	1.03	
Alcohol consumption, g/d				
0	301	1.37	1.06	.01
>0-39	1087	1.35	1.03	
≥40	664	1.57	1.04	
Parental history of diabetes				
Positive	398	1.32	1.05	.14
Unknown	490	1.52	1.05	
Negative	1164	1.42	1.03	
Participants of survey 1‡	520	1.40	1.05	.74
Participants of survey 2	710	1.40	1.04	
Participants of survey 3	822	1.45	1.04	

Abbreviations: See definitions in Table 1 footnote.

**t* Test for equality of means.

†Defined as systolic blood pressure of 160 mm Hg or higher and/or diastolic blood pressure of 95 mm Hg or higher and/or use of antihypertensive medication, given that subjects were aware that they had hypertension.

‡Survey 1 included only participants aged 45 to 64 years.

The WHR was only measured in participants of surveys 2 and 3; therefore, it could not be included in the main models. However, in subgroup analysis, which contained all subjects with WHR measurements (n=1528), the addition of WHR to the model that already included age, survey, and BMI produced changes in the estimates for CRP quartiles between −3.2% and −4.7%, indicating that the fat distribution pattern is important in addition to total body fat.

When logarithmically-transformed CRP levels were entered as a continuous variable into the Cox proportional hazards models, we observed the following HRs for an increase in natural logarithm (ln) CRP concentration of 1.0 mg/L, which corresponds roughly to a change of 1 SD (1.057 ln mg/L): age- and survey-adjusted HR, 1.35; 95% confidence interval (CI), 1.12 to 1.61; age-, survey-, and BMI-adjusted HR, 1.23; 95% CI, 1.01 to 1.49. From the list of potential confounders, only smoking status changed the HR more than 5% when added to the model containing ln CRP, age, survey, and BMI. The effect estimate for ln CRP was 1.15 (95% CI, 0.94-1.41) in this model.

SENSITIVITY ANALYSIS

Exclusion of all subjects who did not know whether they had diabetes at baseline (n=130) hardly influenced the observed HRs, except that the CIs became slightly wider. Therefore, these subjects were included in the main analysis. If all subjects with incident diabetes who were treated only with diet (n=25) and those with missing information on treatment (n=3) were excluded from the analysis, the HRs were increased (adjusted for age, survey, BMI, smoking, and systolic blood pressure; HR for quartile 4 of CRP [≥2.91 mg/L] compared with quartile 1 [≤0.67 mg/L], 1.78; 95% CI, 0.78-4.08).

Table 3. Hazard Ratios (95% CI) for Developing Diabetes by Quartiles of CRP Levels*

Model	Quartile of CRP Level 1	2	3	4	*P* Value for Trend
No. of nondiabetic/diabetic subjects (N = 2052)	505/13	490/21	480/32	476/35	
Model 1	1.0	1.80 (0.90-3.59)	2.85 (1.49-5.43)	2.84 (1.50-5.36)	.003
Model 2	1.0	1.77 (0.89-3.53)	2.72 (1.42-5.21)	2.69 (1.41-5.10)	.007
Model 3	1.0	1.75 (0.87-3.49)	2.69 (1.41-5.15)	2.73 (1.43-5.18)	.006
Model 4	1.0	1.33 (0.66-2.67)	1.83 (0.94-3.56)	1.87 (0.97-3.61)	.09
Model 5	1.0	1.21 (0.60-2.44)	1.50 (0.77-2.94)	1.49 (0.76-2.91)	.33

Abbreviations: CI, confidence interval; CRP, C-reactive protein.
*Model 1 presents the crude hazard ratio. Model 2 is adjusted for age. Model 3 is adjusted for age and survey. Model 4 is adjusted for age, survey, and body mass index. Model 5 is adjusted for age, survey, body mass index, smoking, and systolic blood pressure.

Thirty-four persons developed diabetes during the first 3 years of follow-up. If these subjects and all participants from the third survey, most of whom had a follow-up time of less than 3 years, were excluded, the observed HRs were only slightly smaller than the HRs observed in the whole sample. Furthermore, among those with incident diabetes, we could not observe a trend in CRP values according to the time span between baseline examination and diagnosis. Geometric mean CRP concentrations were 2.3, 2.0, 1.8, 1.9, 2.4, 2.1, and 1.8 mg/L in those diagnosed in 0 to less than 2, 2 to less than 4, 4 to less than 6, 6 to less than 8, 8 to less than 10, 10 to less than 12, and 12 to less than 14 years, respectively.

For 347 subjects who did not have diabetes at baseline and died during follow-up, complete data were available on CRP and all other covariables. If these subjects were included in the Cox proportional hazards models, using *International Classification of Diseases* code 250 mentioned anywhere on the death certificate to identify those who developed incident diabetes (n = 10), the estimated HRs became stronger and the effect was significant even after adjustment for age, survey, BMI, smoking, and systolic blood pressure (HR for quartile 4 of CRP [≥3.29 mg/L] compared with quartile 1 [≤0.71 mg/L], 2.03; 95% CI, 1.07-3.86). The HR was further increased after adjustment for survival status. However, assessment of diabetes incidence through death certificates probably underestimates the true incidence among those who died, since the incidence rate based on death certificate information (5.3 per 1000 person-years) was lower than the incidence rate among the survivors (6.9 per 1000 person-years).

COMMENT

In this large cohort of middle-aged men, drawn randomly from the general population, we observed a significant positive association between raised CRP levels and incident diabetes in age- and survey-adjusted analysis. However, further adjustment for BMI, smoking status, and systolic blood pressure considerably reduced the observed association, and it became nonsignificant. Although this could simply reflect confounding, this observation may also be explained by a causal role of these factors in the induction of an inflammatory state and the development of diabetes mellitus.

The association between inflammatory markers and incident diabetes has been examined only in a few studies so far. In the Atherosclerosis Risk in Communities Study in which 12330 men and women aged 45 to 64 years were followed up for a mean of 7 years, raised white blood cell count, low serum albumin levels, and raised fibrinogen levels significantly predicted the development of incident diabetes mellitus. In a subgroup of 610 individuals, elevated levels of total sialic acid and orosomucoid, essential constituents of most acute-phase reactants, were also associated with the development of incident diabetes. Similar to our results, adjustment for BMI and WHR attenuated these associations, and they remained significant for white blood cell count, orosomucoid, and sialic acid only.[24] In another study conducted in Pima Indians, serum α-globulin, a nonspecific measure of the humoral immune system, increased the risk of diabetes in subjects with initially normal glucose tolerance.[25]

To date, to our knowledge, only 2 prospective studies[26,27] have shown that raised CRP levels are associated with incident diabetes mellitus. In a nested case-control study[26] of 550 middle-aged women followed up for 4 years, the risk of developing type 2 diabetes was increased almost 16-fold if subjects in the top quartile of the CRP distribution at baseline were compared with the bottom quartile. Adjustment for BMI and other covariates considerably attenuated the association, although it remained strong and significant, with a relative risk of 4.2 but wide CIs (95% CI, 1.2-12.0).

In the Cardiovascular Health Study,[27] a prospective study of cardiovascular risk factors in adults 65 years or older, only CRP and none of the other examined markers of inflammation (white blood cell and platelet counts, albumin, fibrinogen, factor VIIIc) was associated with an increased risk of diabetes after adjustment for BMI and other confounders after 3 to 4 years of follow-up (relative risk, 1.8; 95% CI, 1.2-2.9).

Several reasons may explain the lack of statistical significance in multivariate analysis in our study. Although we had included only men, Pradhan et al[26] had studied women only and Barzilay et al[27] had studied men and women. The association between CRP and incident diabetes may be lower in men than in women as previously shown for the association between CRP and cardiovascular events.[28-30] Furthermore, our study may have been hampered by a lack of power due to the relatively small number of incident cases.

PATHOPHYSIOLOGIC CONSIDERATIONS

C-reactive protein is the major acute-phase protein, and increased levels may be caused by chronic or acute infections,[31] smoking,[4,6,9,10] and obesity.[4-6,8,9] The strong association between obesity and increased CRP levels may be explained by the fact that adipose tissue produces significant amounts of various cytokines, such as tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6),[32,33] which regulate the hepatic synthesis of CRP.[34] Both TNF-α and IL-6 have been suggested to be involved in the regulation of lipid and glucose metabolism in adipose tissue and skeletal muscle,[35,36] and these cytokines may thus provide a causal link between obesity and insulin resistance.

The effects of these and possibly other cytokines might also explain the positive association observed between smoking status and incident diabetes.[37] Increased levels of IL-6[38-40] and TNF-α[38] have been found in smokers compared with nonsmokers. Other hypotheses that have tried to explain the link between diabetes mellitus and smoking status suggest that oxidative stress caused by cigarette smoke contributes to the development of endothelial dysfunction, which in turn could lead to insulin resistance.[41,42] In this case, elevation of CRP level might simply represent an epiphenomenon.

The link between systolic blood pressure and low-grade systemic inflammation is less clear. A positive association between systolic blood pressure and CRP has been observed in several cross-sectional studies[5,6,9,10] but could not always be confirmed.[4] Interleukin 6, the major cytokine of the acute-phase response, was associated with systolic blood pressure in women but not men.[43] Furthermore, it remains uncertain whether elevated systolic blood pressure represents the cause or the consequence of the inflammatory state. Thus, further research is necessary to elucidate the biological mechanisms that may explain these associations.

POTENTIAL LIMITATIONS AND STRENGTHS

The present study has several limitations that need to be addressed. We relied on self-reported diagnosis of diabetes mellitus. Participants' reports in general can be considered accurate for diabetes mellitus,[44,45] but a number of people with diabetes are unaware of their condition, because the disease has never been diagnosed by a physician. Thus, our reference group probably contained some subjects with undiagnosed diabetes mellitus, which could have biased our results toward the null. On the other hand, some subjects who were categorized as having incident diabetes probably already had the disease at baseline, which could have biased the results away from the null. In a subgroup of subjects (n=819; 40% of all participants) where hemoglobin A_{1c} and random glucose levels had been assessed at baseline only, 8 subjects (1%) of those classified as nondiabetic at baseline had either a hemoglobin A_{1c} level of greater than 6.5% or a random glucose level of 200 mg/dL or higher (≥11.1 mmol/L). Of these, 2 had known diabetes at follow-up and 6 were classified as nondiabetic at follow-up. Thus, the impact of this misclassification is probably small. Furthermore, exclusion of all subjects in whom diabetes had been diagnosed within the first 3 years after the baseline examination did not materially affect the association. In addition, follow-up was not complete for all participants of the original study who were still alive in 1998, which might have introduced a selection bias.

Furthermore, misclassification of exposure cannot be excluded since only one CRP measurement was available, and repeatability of CRP is only moderate (W.K., M. Sund, MS, M.F., H.L., W. L. Hutchinson, PhD, M. B. Pepys, FRS, unpublished data, 2002). Acute infections lead to temporarily increased CRP levels, which do not represent the true long-term basal CRP value. However, in this study only 2% and 3%, respectively, of future diabetic and nondiabetic subjects had CRP values greater than 10 mg/L.

Finally, we were unable to distinguish between different types of diabetes mellitus. Since all cases occurred in men 45 years and older and since only a few cases were treated with insulin alone, it can be assumed that most of our subjects had developed type 2 diabetes. The strengths of our study are primarily its prospective design and the representativeness of the cohort, based on a random sample of the general population.

In conclusion, we report a positive association between levels of CRP and incident diabetes mellitus, which suggests a role for inflammation in the etiology of diabetes mellitus. Adjustment for established risk factors for diabetes and cardiovascular disease, such as obesity, smoking, and systolic blood pressure, significantly attenuated the observed association, which may indicate that the effect of these factors in the pathogenesis of diabetes is mediated, at least in part, through an inflammatory process. Increased levels of proinflammatory cytokines, such as IL-6, may explain the link between these risk factors, increased CRP levels, and a higher incidence of diabetes mellitus.[26] Further insight into the mechanisms involved in the etiology of diabetes and the specific effects of proinflammatory cytokines and acute-phase proteins will be essential for the development of new preventive strategies for diabetes mellitus.

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