

Risk of Type 2 Diabetes Attributable to C-Reactive Protein and Other Risk Factors

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OBJECTIVE — To calculate the population-attributable risk (PAR) of C-reactive protein (CRP) and other risk factors for type 2 diabetes.

RESEARCH DESIGN AND METHODS — The Rotterdam Study is a population-based, prospective follow-up study among 7,983 participants aged ≥ 55 years. Risk factors including serum CRP were determined at baseline. Participants with diabetes at baseline were excluded, and the cohort was followed for a mean of 10.8 years. The hazard ratio (HR) and PAR for diabetes were computed for all studied risk factors.

RESULTS — Serum CRP > 1 mg/l (HR 1.67, PAR 0.33), BMI > 25 kg/m² (HR 2.51, PAR 0.51), waist circumference > 102 for men and > 88 cm for women (HR 1.36, PAR 0.14), current smoking (HR 1.16, PAR 0.03), age > 65 years (HR 1.35, PAR 0.15), and family history of diabetes (HR 1.87, PAR 0.16) were related to diabetes and contributed to the risk of the disease. Serum CRP was a greater contributor to the risk of diabetes in women than in men (PAR values of 0.37 vs. 0.28, respectively). Age and current smoking PARs were not statistically significantly contributing to the risk of diabetes in women. Combined PAR was 0.80 (95% CI 0.74–0.85) for all six studied risk factors and 0.71 (0.64–0.78) for modifiable risk factors (serum CRP, BMI, waist circumference, and current smoking).

CONCLUSIONS — High CRP is one of the major contributors to the risk of type 2 diabetes. The contribution of modifiable risk factors to the risk of diabetes is considerable.

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There is a growing body of evidence that low-grade systemic inflammation enhances the risk of type 2 diabetes (1). Furthermore, anti-inflammatory medication may prevent diabetes or delay the onset of the disease (2). Whether inflammation is a major contributor to the risk of diabetes is not yet clear.

Population-attributable risk (PAR) is a relevant measure used to judge the public health impact of different risk factors (3). The PAR of a risk factor for a disease is the proportion of those with the disease that is due to that risk factor. The PAR depends on both the relative risk estimate and the prevalence of the risk factor.

C-reactive protein (CRP), a marker of inflammation, is independently associated with the development of diabetes (1,4,5) and can be reduced by the use of anti-inflammatory medications (6). Therefore, the PAR of serum CRP for diabetes can be used to estimate the contribution of inflammation to the risk of diabetes. To our knowledge, there is no previously published study on the PAR of high serum CRP for diabetes. We sought to quantify the contribution of a number of risk factors including serum CRP to the risk of diabetes in the Rotterdam Study, a large population-based prospective cohort study in Caucasians aged ≥ 55 years.

RESEARCH DESIGN AND METHODS

The study was conducted within the framework of the Rotterdam Study, an ongoing prospective, population-based cohort study on determinants of a number of chronic diseases. The Rotterdam Study has been described in detail elsewhere (7). In brief, all inhabitants of Ommoord, a district of Rotterdam in the Netherlands, who were aged ≥ 55 years were invited to participate in this study. Of 10,275 eligible individuals, 7,983 agreed to participate (78%).

The baseline examinations took place from 1990 to 1993. Follow-up for clinical events started at baseline, and follow-up examinations were carried out periodically in 1995–1996, 1997–1999, and 2000–2005. In addition, participants were continuously monitored for major events through automated linkage with files from general practitioners and pharmacies working in the study district of Ommoord. Information on vital status was obtained regularly from municipal health authorities in Rotterdam. For the present study, follow-up data were available until 1 October 2005. Written informed consent was obtained from all participants, and the medical ethics committee of the Erasmus Medical Center approved the study.

Serum CRP

High-sensitivity CRP was measured in nonfasting serum samples kept frozen at -20°C by use of Rate Near Infrared Particle Immunoassay (Image Immunochemistry System; Beckman Coulter). This method has been described in more detail elsewhere (1). Serum samples were stored for ~ 10 years at -20°C until the measurements were carried out in 2003–2004. We compared these CRP measurements with CRP measurements in the serum samples stored at -80°C in a random sample of 29 participants. The Spearman correlation coefficient was 0.99 between the CRP serum level measurements carried out on samples kept at -20°C and -80°C ($P < 0.001$).

Diabetes

At baseline, participants were defined as prevalent cases with type 2 diabetes when they had nonfasting glucose level > 11.1

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Abbreviations: CRP, C-reactive protein; PAR, population-attributable risk.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—Baseline characteristics of participants in different categories of serum CRP

Risk factor	Serum CRP			P value
	<1 mg/l	1–3 mg/l	>3 mg/l	
n	1,717	2,702	2,516	—
Men (%)	40.5	64.5	57.2	<0.001
BMI (kg/m ²)	24.9 ± 3.2	26.5 ± 3.4	26.9 ± 3.6	<0.001
Waist circumference (cm)	85.9 ± 10.4	90.1 ± 10.2	93.4 ± 9.5	<0.001
Current smoking (%)	16.6	19.5	28.7	<0.001
Age (years)	67.3 ± 8.5	68.5 ± 8.8	72.9 ± 9.9	<0.001
Family history of diabetes (%)	21.3	21.3	19.8	0.37
HDL cholesterol (mmol/l)	1.44 ± 0.39	1.36 ± 0.36	1.29 ± 0.35	<0.001
Systolic blood pressure (mmHg)	134.0 ± 21.4	139.0 ± 21.7	142.0 ± 22.3	<0.001
Diastolic blood pressure (mmHg)	72.8 ± 11.3	74.2 ± 11.3	74.1 ± 11.9	<0.001
Hypertension (%)	23.5	33.7	42.7	<0.001

Data are means ± SD or n (%).

mmol/l, oral glucose tolerance test >11.1 mmol/l, or when they were using antidiabetes medications. Incident cases of type 2 diabetes were diagnosed based on a fasting plasma glucose level ≥7.0 mmol/l, a random (nonfasting) plasma glucose level ≥11.1 mmol/l, use of oral antidiabetes medications, or use of insulin or treatment by diet and registered by a general practitioner as having diabetes (1).

Population for analysis

We excluded 861 prevalent diabetic participants and 187 participants who did not provide any information on their glucose levels at baseline. The population for analysis consisted of 6,935 participants. Of these, serum CRP level was available in 5,901, BMI in 6,136, waist circumference in 5,837, and smoking status in 6,765 participants.

Statistical analysis

High serum CRP (1,4), overweight (8), truncal fat distribution (9,10), physical inactivity (11), smoking (12–14), aging, and family history of diabetes (15) have been reported as risk factors for diabetes. Established cutoff points were used to dichotomize continuous covariates into normal and elevated levels. On this basis, serum CRP ≥1 mg/l, BMI ≥25 kg/m², waist circumference ≥102 cm for men and ≥88 cm for women, and age ≥65 years were considered risk factors for diabetes. Smoking was assessed as current smoking versus nonsmoking, and family history of diabetes was considered positive in the presence of diabetes in parents, children, or any of the siblings. A Cox regression analysis was used to investigate the association of risk factors with incidence of diabetes.

PARs and 95% CIs were calculated by the use of the Interactive Risk Assessment Program developed by Dr. Mitchell Gail (U.S. National Cancer Institute, 2002) (16–19). A PAR adjusted for confounding is estimated by the following:

$$PAR = 1 - \sum_{i=1}^I \sum_{j=1}^J \rho_{ij} R_{ij}^{-1}$$

where the relative risk is

$$R_{ij} = \frac{\Pr(D = 1 | X = \chi_i, C = c_j)}{\Pr(D = 1 | X = \chi_1, C = c_j)}$$

and

$$\rho_{ij} = \Pr(X = \chi_i, C = c_j | D = 1)$$

given $D = 1$ denoting presence of disease, X denoting exposure with i levels, and C denoting a confounder with j levels. The relative risk is estimated from a multivariate Poisson model (18).

The PAR for a combination of risk factors corresponds with the proportion of the disease that can be attributed to any of the studied risk factors. The combined PAR is not a simple product of summing up the single PARs. A diseased case can simultaneously be attributed to more than one risk factor. As a result, the fraction of the population that is attributed to or prevented by each risk factor overlaps with other risk factors. Hence, the combined PAR is usually lower than the sum of individual PARs. To estimate the proportion of the disease that is exclusively attributed to a specific risk factor, we calculated the combined PAR in the presence and absence of this risk factor. The difference is the so-called “extra attributable risk,” which indicates the proportion of

the disease that can be attributed exclusively to this specific risk factor (20).

To provide a similar study population for different analysis and to increase the statistical power, we imputed missing data using the expectation maximization method in SPSS 11.0, which is based on the correlations between each variable with missing values and all other variables.

RESULTS— Table 1 shows the baseline characteristics of the studied population in tertiles of serum CRP.

During a mean follow-up time of 9.9 years (interquartile range 6.5–13.2), diabetes developed in 645 subjects (incidence rate 9.4 per 1,000 person-years). Table 2 shows the proportion of the participants who were exposed to each risk factor and their association with risk of type 2 diabetes. BMI (>25 kg/m²) and family history of diabetes were the strongest risk factors. High serum CRP (>1 mg/l) had a greater hazard ratio (HR) in women (1.77) than in men (1.42), and current smoking had a greater HR in men (1.37) than in women (1.10). However, the differences between HRs were not significant. The association between age (>65 years) and diabetes was stronger in men (HR 1.64) than in women (HR 1.15), and the difference between HRs was significant (P for interaction <0.05).

Multivariate-adjusted PAR was 0.33 (95% CI 0.21–0.46) for high serum CRP. The PAR of high serum CRP for diabetes was 0.17 (0.08–0.25) and 0.08 (0.02–0.15) when cutoff points of 2 and 3 mg/l were used, respectively. Moreover, the PAR was 0.17 for the highest versus the lowest and 0.32 for the top two tertiles versus the lowest tertile of serum CRP. High BMI (>25 kg/m²) was the main contributor to the risk of diabetes (PAR 0.51 [95% CI 0.41–0.60]) (Table 3).

Collectively, studied risk factors contributed to 80% (95% CI 74–85) of the risk of diabetes. Modifiable risk factors (serum CRP, BMI, waist circumference, and current smoking) contributed to 71% of the risk, suggesting that more than two-thirds of incident diabetes cases might have been prevented if all the above risk factors were eliminated (Table 4). Moreover, we estimated the combined PAR for modifiable risk factors in the absence of each risk factor to estimate the extra attributable risk. Exclusion of serum CRP decreased the combined PAR from 0.71 to 0.58, indicating that the extra attributable risk was 0.13 for high serum CRP (Table 4).

Table 2—Percent exposed and multivariate-adjusted* HR of diabetes associated with risk factors

Risk factor	Exposed (%)		HR (95% CI) for diabetes		
	Men (n = 2,733)	Women (n = 4,202)	All participants	Men	Women
CRP >1 mg/l	74.8	75.9	1.67 (1.34–2.09)	1.42 (1.11–2.12)	1.77 (1.30–2.40)
BMI >25 kg/m ²	61.2	67.0	2.51 (2.00–3.16)	2.57 (1.86–3.56)	2.44 (1.76–3.39)
High waist circumference†	17.6	53.4	1.36 (1.14–1.63)	1.43 (0.97–1.68)	1.47 (1.14–1.88)
Current smoking	29.7	17.2	1.16 (0.96–1.40)	1.37 (0.93–1.56)	1.10 (0.84–1.44)
Age >65 years	60.7	67.9	1.35 (1.14–1.59)	1.64 (1.26–2.11)	1.15 (0.92–1.42)
Family history of diabetes	18.8	22.0	1.87 (1.59–2.20)	1.86 (1.44–2.40)	1.88 (1.52–2.33)

*Model adjusted for CRP, BMI, waist circumference, current smoking, age, and family history. †Waist circumference >102 cm for men and >88 cm for women.

CONCLUSIONS— In this study, we found that high serum CRP is a major contributor to the risk of type 2 diabetes, independent of the other established risk factors. In addition, we observed that established risk factors account for a large proportion (80%) of the risk of type 2 diabetes in the general population aged ≥55 years.

Our study underscores chronic inflammation as a major contributor to the risk of diabetes by showing that one-third of the cases with diabetes are attributed to high serum CRP. Serum CRP, a marker of chronic low-grade inflammation, is a novel risk factor for diabetes. PAR is mostly estimated for the risk factors of which a causal role is evidenced. High serum CRP predicts diabetes, and a growing body of evidence supports the causal role of CRP (1,2,4). Hence, it would be logical to attribute a part of the risk of diabetes to chronic low-grade inflammation. However, estimation of PAR for a new risk factor when the causal role is not yet widely accepted illustrates the potential impact of the risk factor, were it later accepted to be causal (20).

Serum CRP is a marker of inflammation but is also closely related to adiposity. This may raise doubt about whether CRP is a marker of inflammation or adiposity. We believe that even the variation of serum CRP, correlated with obesity, indicates an inflammatory state. The increased level of serum CRP in obese individuals is due to increased secretion of interleukin-6 and tumor necrosis factor- α in adipocytes, which regulate CRP production in hepatocytes and induce a chronic inflammatory state (21).

We adjusted the association for age, BMI, and waist circumference as potential confounders. However, the covariates were dichotomized, and dichotomization increases the likelihood of residual confounding. To estimate the magnitude of

the residual confounding, we introduced age, BMI, and waist circumference as covariates with 10 categories to the model. Estimated PAR for high serum CRP slightly attenuated to 0.32 (95% CI 0.20–0.45). Therefore, residual confounding by age and obesity in our findings should be trivial.

To obtain a reasonable estimate of the PAR, one should use a cutoff point that could be achieved in practice (22). For serum CRP, however, no cutoff point has been recommended in relation to the risk of diabetes. The American Heart Association suggests two cutoff points of 1 and 3 mg/l in relation to cardiovascular risk (23). When we used the cutoff point of 1 mg/l to dichotomize serum CRP, 75% of our population was exposed, which may seem to be overestimating. However, where over 61% of men and 67% of women were overweight or obese, it is not too far to consider serum CRP, which is highly correlated with BMI, to be high in 75% of our population in regard to diabetes.

A disease can simultaneously be at-

tributed to or prevented by more than one risk factor. Therefore, the fractions of the disease, which are attributed to different risk factors, overlap with each other and cannot be simply summed up. To estimate the proportion of the disease that is attributed to a certain number of risk factors, combined PAR should be estimated. Our combined PAR showed that the majority of diabetes cases are preventable. This finding is in agreement with other studies. Hu et al. (24) reported that 91% of diabetes cases in women can be attributed to overweight, poor diet, lack of exercise, smoking, and abstinence from alcohol. Hu et al. studied diet and physical activity, which were not present in our study, and their study was restricted to women. This may explain why they found a slightly higher estimate for the combined PAR. However, they did not study any marker of inflammation.

Extra attributable risk was 0.13 for high serum CRP. This should not be confused with the single adjusted PAR, which was 0.33 for high serum CRP. Single PAR indicates the fraction of cases that can be

Table 3—Multivariate-adjusted* PARs of different risk factors for diabetes

	All participants	Men	Women
CRP (3rd vs. 1st tertile)	0.17 (0.11–0.23)	0.16 (0.06–0.26)	0.18 (0.10–0.25)
CRP (2nd and 3rd vs. 1st tertile)	0.32 (0.22–0.42)	0.23 (0.8–0.39)	0.39 (0.26–0.53)
CRP >1 mg/l	0.33 (0.21–0.46)	0.28 (0.10–0.47)	0.37 (0.20–0.53)
BMI >25 kg/m ²	0.51 (0.41–0.60)	0.50 (0.37–0.63)	0.51 (0.37–0.64)
High waist circumference†	0.14 (0.06–0.22)	0.07 (–0.01 to 0.14)	0.22 (0.08–0.35)
Current smoking	0.03 (–0.01 to 0.07)	0.05 (–0.02 to 0.13)	0.02 (–0.03 to 0.06)
Age >65 years	0.15 (0.06–0.24)	0.25 (0.13–0.37)	0.06 (–0.07 to 0.19)
Family history of diabetes	0.16 (0.11–0.20)	0.15 (0.08–0.21)	0.16 (0.10–0.23)

Data are PAR (95% CI). *Model adjusted for all present covariates: CRP, BMI, waist circumference, current smoking, age, and family history. †Waist circumference >102 cm for men and >88 cm for women.

Table 4—Combined PAR of all modifiable risk factors* and combined PAR of all risk factors with one deleted

Risk factor	All participants	Men	Women
Total	0.80 (0.74–0.85)	0.79 (0.71–0.87)	0.80 (0.73–0.87)
Modifiable risk factors*	0.71 (0.64–0.78)	0.65 (0.57–0.79)	0.75 (0.66–0.83)
Deleted factor			
CRP >1 mg/l	0.58 (0.50–0.66)	0.55 (0.43–0.67)	0.61 (0.51–0.71)
BMI >25 kg/m ²	0.44 (0.33–0.55)	0.39 (0.22–0.55)	0.51 (0.37–0.66)
High waist circumference†	0.68 (0.59–0.76)	0.66 (0.54–0.78)	0.69 (0.58–0.80)
Current smoking	0.70 (0.63–0.84)	0.67 (0.55–0.78)	0.74 (0.66–0.83)

Data are PAR (95% CI). *CRP, BMI, waist circumference, and current smoking entered to the model. The results are also adjusted for age and family history of diabetes. †Waist circumference >102 cm for men and >88 cm for women.

prevented by lowering serum CRP, assuming that the other risk factors remain unchanged. However, extra attributable risk suggests that if a hypothetical prevention program has eliminated all other studied risk factors, lowering serum CRP still can prevent 13% of incident diabetes cases. The difference between the single PAR and the extra attributable risk is due to those cases that were alternatively attributed to high serum CRP and other risk factors. These risk factors may act in the same pathway with CRP, leading to the development of diabetes. For instance, recent studies suggest that at least a part of the association of obesity (4) and smoking (25,26) with diabetes may be through low-grade chronic inflammation.

Caution should be taken in interpreting the PAR in practice. In computing PARs, we assume that all participants who are labeled as exposed will shift to the nonexposed group without causing any change in the risk factor distribution in the nonexposed group. Moreover, we assume that the risk of the disease decreases instantly after the intervention. In practice, however, the effect of an intervention is likely to be different. First, a part of the population succeeds to modify the risk factor but cannot avoid it. Second, the risk factor distribution will change in the nonexposed population. Third, the risk of the disease does not decrease instantly after removing the risk factor. Therefore, one should be careful in translating the PAR from such studies into practice. Furthermore, a high combined PAR does not mean that no additional risk factors can be detected for diabetes. The diabetes cases that are attributed to the current risk factors can alternatively be attributed to a novel risk factor, when the novel risk factor interacts with the currently known risk factors.

Our study has the advantage of hav-

ing a large sample size, a long follow-up period, and a considerable number of incident diabetes cases. However, a limitation is that physical activity was not measured in our study at baseline. Inclusion of physical activity in the models will probably modify the HR and the PAR of other risk factors. One other limitation was that our study population was >55 years old, which may raise a debate on the generalizability of our results. To examine the issue, we divided the population to subgroups of <65 and >65 years old. The PAR estimates were nearly the same for both groups (32.3 vs. 32.9%). This is not surprising since the association between serum CRP and diabetes was stronger in subjects age <65 years, and high serum CRP (>1 mg/l) was more prevalent in subjects aged >65 years. This shows that PAR estimates are not modified by age and that our findings can be extrapolated to other age-groups.

In conclusion, high CRP is a major contributor to the risk of type 2 diabetes. The modifiable risk factors studied contribute to two-thirds of the risk of diabetes. A large part of the diabetes cases can be prevented if the modifiable risk factors were eliminated.

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