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C-reactive protein and albuminuria
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C-reactive protein and microalbuminuria differ in their associations with various domains of vascular disease


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Abstract

Background. C-reactive protein (CRP) and microalbuminuria (MA) have been identified as risk markers for cardiovascular disease (CVD). We questioned whether CRP and MA are similar markers of vascular disease in different regions of the vascular tree like the heart, kidneys and extremities or that they differ with their relationships in these vascular beds.

Methods and Results. Baseline levels of CRP and urinary albumin were measured in 6,669 non-diabetic participants in the PREVEND study, a Dutch cohort derived from the general population. We defined three domains of vascular disease: coronary heart disease (myocardial infarction or infarct pattern on the ECG), renal insufficiency (creatinine clearance <60 ml/min) and peripheral artery disease (ankle brachial index <0.9 or lower limb revascularisation). The prevalence of an elevated CRP (27.7 vs 17.9%) and MA (17.5 vs 10.4%) were increased in subjects with vascular disease as compared to subjects without CVD. The prevalence of an elevated CRP was equal in subjects with either coronary heart disease, renal insufficiency or peripheral artery disease (28.4 vs 29.5 vs 26.0%, NS), whereas MA was most prevalent in subjects with coronary heart disease (22.5 vs 12.8 vs 14.9%, P<0.05). Using multivariate analyses, CRP was independently associated with all three domains of vascular disease, whereas MA was independently associated with coronary heart disease only. In addition, we found synergistic contributions of an elevated CRP and older age to the risk of vascular disease in all three domains.

Conclusions. Thus, CRP and microalbuminuria are risk markers for vascular disease, each showing a different risk profiling for different vascular beds.

Introduction

Risk factors for cardiovascular (CV) disease, like type 2 diabetes and hypertension, typically affect multiple organs and organ systems as the heart, brain, kidneys and peripheral arteries. The magnitude of associations between CV risk factors and organs affected most may differ. Recently, novel CV risk markers have been introduced as predictors of cardiovascular morbidity and mortality, such as C-reactive protein (CRP) and microalbuminuria.

CRP is a sensitive marker of inflammation. Inflammation, either systemically or at local sites, may underlie the atherosclerotic process resulting in vascular end-organ damage and it applies to multiple vascular beds. Indeed, slight increases in serum CRP levels are associated with an increased risk for damage in different vascular beds, including the heart, brain, kidneys and lower extremities, however, CRP is not an independent risk marker for CV disease in some reports.
Microalbuminuria, classically defined as a urinary albumin excretion of 30-300 mg/24h, has also been identified as a risk marker for CV disease. Like CRP, microalbuminuria is a powerful marker of arterial disease in various vascular beds. Therefore, its appearance in the urine does not only reflect early vascular or glomerular disease in the kidney but microalbuminuria also indicates early vascular or endothelial damage in the vascular tree in general. Indeed, microalbuminuria is related to subclinical atherosclerosis and indicates increased risk for vascular disease in the heart, brain, kidney and lower extremities.

The associations of both CRP and microalbuminuria with vascular disease in different vascular beds have not been investigated. A number of studies have shown a link between the two parameters in non-diabetic, and in diabetic and obese subjects. These studies suggested that microalbuminuria and CRP reflect a common link with respect to vascular disease. In the current cross-sectional study we had the opportunity to study both CRP and microalbuminuria with respect to various domains of vascular disease in a sample of the general population. Therefore, we investigated the relation between CRP, microalbuminuria and vascular disease in various vascular beds such as the heart, kidney and lower extremities. We secondly investigated whether these associations were different for the different vascular beds we have evaluated.

Methods

Study Population and design

The PREVEND study (Prevention of REnal and Vascular ENdstage Disease) is a population-based cohort study. Baseline data were collected in 1997/1998 in male and female subjects aged 28-75 years living in the city of Groningen, The Netherlands. The PREVEND study is designed to investigate the natural course of microalbuminuria and its relationship with renal and cardiovascular disease. Details of the study design and methods have been described elsewhere. In short, all inhabitants were asked to send in a morning urine sample and to fill in a short questionnaire on demographics and cardiovascular medical history. All subjects with a urinary albumin concentration >10 mg/L and a randomly selected sample of subjects with a urinary albumin concentration <10 mg/L were invited to perform two visits at the outpatient clinic. Subjects who were pregnant or using insulin were excluded. We eventually performed baseline measurements in a total of 8,592 invited subjects: the sample of this study. This study was approved by the medical ethics committee and conducted in accordance with the guidelines of the declaration of Helsinki. All participants who attended the outpatient clinic gave written informed consent.
The two visits included the following measurements: anthropometric measurements (height, weight, waist and hip circumferences), blood pressure measurements at the first and second visit respectively, ankle pressure measurements, electrocardiograph recordings, fasting blood samples and the collection of 2x24 hours urine samples after thorough oral and written collection instruction. All 8,592 subjects completed an extensive questionnaire on demographics, cardiovascular and renal and family medical history, and drug use.

Laboratory methods

Urinary albumin concentrations were determined by nephelometry with a threshold of 2.3 mg/L and intra- and inter-assay coefficients of variation of less than 2.2% and 2.6%, respectively (Dade Behring Diagnostic, Marburg, Germany). High sensitive CRP was also determined by nephelometry with a threshold of 0.175 mg/L and intra- and inter-assay coefficients of less than 4.4% and 5.7%, respectively (BNII N, Dade Behring, Marburg, Germany). CRP levels below the detection level were scored as 0.18 mg/L. Plasma glucose, serum cholesterol, serum and urinary creatinine were determined by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, New York, U.S.A.). Urinary leukocyte and erythrocyte measurements were done by Nephur-test+leuco sticks (Boehringer Mannheim, Mannheim, Germany).

Calculations

Systolic and diastolic blood pressure was calculated as the average of the last two measurements of both visits. Body mass index was calculated as the ratio between height (kg) and the square of height (m) (kg/m$^2$). Urinary albumin excretion was calculated as the mean of two 24 hours urine collections. Creatinine clearance was calculated as urine volume (ml) per minute times the urinary concentration of creatinine and divided by the serum concentration of creatinine. The mean of two values derived from both 24 hours urine collections was used for analysis.

Data handling and definitions

Urinary albumin measurements were considered unreliable in 451 subjects with either leukocyturia or erythrocyturia (erythrocytes >50 cells/mm$^3$ or leukocytes >75 cells/mm$^3$, or leukocytes=75 cells/mm$^3$ and erythrocytes >5 cells/mm$^3$). We also excluded 312 subjects with diabetes mellitus (fasting glucose ≥7.0 mmol/L or non-fasting glucose ≥11.1 mmol/L or antidiabetic therapy) and 65 with known renal disease. We excluded 79 subjects with macroalbuminuria (albuminuria
>300 mg/24h) and 270 subjects with a CRP level >10 mg/L. We also excluded those subjects with vascular damage in more than one organ system (n=82). We missed 167 cases because of missing data on one or more of the above exclusion criteria.

Missing data on coronary heart disease, creatinine clearance and incomplete ankle pressure measurements were present (n=123, 58 and 317 respectively). A separate analysis was performed in which the effect of missing data was evaluated by including an available/not available term, which did not change the estimated effects. All together 6,669 subjects were eligible for analysis.

**Domains of vascular disease.** We determined vascular disease according to three different vascular beds, i.e. the heart, the kidney and the lower extremities.

**The heart.** Established coronary heart disease was defined as prior myocardial infarction with hospitalisation reported by questionnaire and/or an infarct pattern on the electrocardiogram, defined by Minnesota codes 1.1 and 1.2. Standard 12-lead electrocardiograms were recorded with Cardio Perfect equipment (Cardio Control, Delft, the Netherlands), stored digitally and classified according to Minnesota code using the computer program MEANS (Modular ECG Analysis System).

**The kidney.** We used measured creatinine clearance <60 ml/min as the definition for renal insufficiency. To avoid bias due to primary renal disease, we excluded subjects with leukocyturia and/or erythrocyturia, known renal disease, diabetes mellitus, and macroalbuminuria. In addition, we tested the robustness of our results regarding renal insufficiency by defining other criteria, e.g. the sex-specific 5th percentile values of creatinine clearance, creatinine clearance corrected for body surface area (BSA) and the sex-specific 95th percentile value of serum creatinine for renal insufficiency. We also calculated our results with creatinine clearance corrected for BSA according to the K/DOQI guidelines. These steps, however, did not change the results of this study.

**The lower extremities.** Peripheral artery disease was defined as an ankle-brachial index < 0.9 in at least one leg and/or prior arterial surgery of the lower limbs. At the first visit, while the participant was in a supine position, systolic blood pressure was measured each minute with an automatic Dynamap XL Model 9300 series device at the right brachial artery (10 times total). Within the first 5 minutes, systolic ankle pressure at each leg was measured at the same time a brachial pressure was performed. For ankle pressure measurements, the posterior tibial artery was measured using an 8-MHz continuous-wave Doppler probe (Huntleigh Model D900, Huntleigh Diagnostics) and a random-zero sphygmomanometer. The ankle-brachial index was calculated as the ratio of the systolic blood pressure of the ankle and arm for each leg. The lowest ankle-brachial index in either leg was used in the analysis.
Risk factors and indicators. Microalbuminuria was defined as a urinary albumin excretion 30-300 mg per 24 hours. An elevated CRP level was defined as >3 mg/L. Other cardiovascular risk factors were also dichotomised and defined as follows: age above 60 years, male sex, hypertension, hypercholesterolemia, obesity, elevated glucose, and smoking. Family history was also considered.

Table 1. Population characteristics: prevalence of risk factors according to elevated C-reactive protein levels and microalbuminuria.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Overall</th>
<th>Elevated CRP</th>
<th>Microalbuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (absolute, %)</td>
<td>6669</td>
<td>5138 (80.9)</td>
<td>1210 (19.1)</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>0.8 (0.4-1.5)</td>
<td>4.8 (3.7-6.5)</td>
<td>1.0 (0.5-2.3)</td>
</tr>
<tr>
<td>Albuminuria (mg/24h)</td>
<td>8.5 (6.1-14.3)</td>
<td>10.2 (6-21)†</td>
<td>8.1 (5.9-12.1)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>48.0 (12.3)</td>
<td>47.3 (12.1)</td>
<td>51.0 (12.8)†</td>
</tr>
<tr>
<td>Age &gt;60 yr (%)</td>
<td>19.9</td>
<td>17.9</td>
<td>28.4†</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>48.1</td>
<td>52.9</td>
<td>45.8†</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>127 (19)</td>
<td>126 (19)</td>
<td>133 (21)†</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>73 (10)</td>
<td>73 (10)</td>
<td>75 (10)†</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>27.8</td>
<td>24.9</td>
<td>38.9†</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.6 (1.1)</td>
<td>5.5 (1.1)</td>
<td>5.9 (1.1)†</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>23.6</td>
<td>21.6</td>
<td>31.5†</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.8 (3.9)</td>
<td>25.3 (3.6)</td>
<td>27.5 (4.6)†</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>13.5</td>
<td>10.4</td>
<td>25.6†</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.7 (0.6)</td>
<td>4.7 (0.6)</td>
<td>4.8 (0.7)†</td>
</tr>
<tr>
<td>Elevated glucose (%)</td>
<td>3.1</td>
<td>2.6</td>
<td>4.8†</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>37.8</td>
<td>35.4</td>
<td>45.9†</td>
</tr>
<tr>
<td>Family history (%)</td>
<td>18.4</td>
<td>17.6</td>
<td>21.4†</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) for normally distributed parameters or median (25-75th percentile) for skewed distributions. †P<0.005 (Elevated CRP yes versus no), ‡P<0.005 (Microalbuminuria yes versus no).
hypertension (diastolic blood pressure >90 mmHg or systolic blood pressure >140 mmHg or antihypertensive use), hypercholesterolemia (total serum cholesterol >6.5 mmol/L or lipid-lowering therapy), obesity (body mass index >30 kg/m²), elevated plasma glucose (plasma glucose 6.1-7.0 mmol/L) as an approximate of glucose intolerance, positive cardiovascular family history (first-grade relatives with established cardiovascular events before the age of 55), and smoking (current cigarette smoking or quit smoking <1 year).

Table 2. Prevalence of risk factors, including CRP and microalbuminuria, according to different vascular beds.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Vascular disease</th>
<th>Domains of vascular disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td></td>
<td>Coronary heart disease</td>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>N</td>
<td>5870</td>
<td>799</td>
</tr>
<tr>
<td>Elevated CRP, %</td>
<td>17.9</td>
<td>27.7&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Microalbuminuria, %</td>
<td>10.4</td>
<td>17.5&lt;sup&gt;x&lt;/sup&gt;</td>
</tr>
<tr>
<td>Age &gt; 60 yr, %</td>
<td>17.1</td>
<td>40.3&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>51.3</td>
<td>55.6&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>25.7</td>
<td>42.8&lt;sup&gt;&lt;sup&gt;x&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>22.0</td>
<td>35.3&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>37.5</td>
<td>39.8</td>
</tr>
<tr>
<td>Obesity, %</td>
<td>13.3</td>
<td>14.7</td>
</tr>
<tr>
<td>Elevated glucose, %</td>
<td>2.9</td>
<td>4.6&lt;sup&gt;&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Positive family history, %</td>
<td>18.2</td>
<td>19.1</td>
</tr>
</tbody>
</table>

In this table, the prevalence of risk factors among subjects without or with vascular disease is compared (left). The presence of vascular disease is subsequently divided into coronary heart disease, renal insufficiency and peripheral artery disease (right).

- <sup>a</sup> Significance levels of absent versus present vascular disease.
- <sup>b</sup> Coronary heart disease versus renal insufficiency.
- <sup>c</sup> Coronary heart disease versus peripheral artery disease.
- <sup>d</sup> Renal insufficiency versus peripheral artery disease.

† P<0.05, ‡ P<0.01, ¶ P<0.005.
Statistical analysis

Analyses were performed using the statistical package SPSS 10.1 (SPSS, Chicago, IL, U.S.A.). The significance level was determined at \( P < 0.05 \). Continuous data are reported as mean with standard deviation. In case of a skewed distribution, the median with the interquartile range is presented (CRP and albuminuria). The prevalence of all risk factors were compared between all three vascular domains and also compared with subjects with no vascular disease. For comparison between prevalences, \( X^2 \) analysis was carried out.

Logistic regression analysis was used, in which all three vascular domains were analysed separately as the independent variable. Subjects with damage in more than one vascular system were excluded. Crude, age and sex adjusted and odds ratios adjusted for all risk factors are presented. Each analysis was performed with and without adding CRP or microalbuminuria into the analysis to determine their relative contributions to vascular disease. Finally, a multivariate analysis, including tests for interactions between either CRP or microalbuminuria and other risk factors on the risk of vascular disease, was performed. Interaction terms were considered statistically significant at a \( P \) value of <0.1.

Results

Coronary heart disease was present in 4.9% of the subjects, renal insufficiency in 2.6% and peripheral artery disease in 4.5%. Table 1 shows the overall prevalence of an elevated CRP (19.1%) and microalbuminuria (11.2%) as well as the classical risk factors according to the absence or presence of an elevated CRP and microalbuminuria. The table shows that an elevated CRP level was associated with an increased age, female gender, hypertension, hypercholesterolemia,
obesity, elevated glucose level, increased prevalence of smoking and positive family history of cardiovascular disease. This pattern was also observed in subjects with microalbuminuria. In contrast however, microalbuminuria was not associated with a positive family history of CV disease and smoking. Also, microalbuminuric subjects were more frequently male.

Table 2 shows the prevalence of elevated CRP and microalbuminuria as well as the CV disease risk factors according to the absence or presence of overall vascular disease (left columns). The prevalence of elevated CRP (27.7 vs 17.9%) and microalbuminuria (17.5 vs 10.4%) was increased in subjects with vascular disease as compared to subjects without disease (both $P<0.005$). Furthermore, subjects with vascular disease were older, male, hypertensive, hypercholesterolemic and more subjects had an elevated glucose level. We further subdivided the presence of vascular disease in the three domains of vascular disease (right columns). There was a clear distinction between CRP and microalbuminuria with respect to their associations with damage in the different vascular beds. The prevalence of elevated CRP was not different between vascular regions (heart vs kidney vs peripheral arteries: 28.4 vs 29.5 vs 26.0%, NS), whereas microalbuminuria was most prevalent in subjects with coronary heart disease (22.5 vs 12.8 vs 14.9%, $P<0.05$, respectively). The prevalence of older age, hypertension, hypercholesterolemia, elevated glucose level and a positive family history were similar among the three domains of vascular disease. Male gender and obesity were clearly more prevalent in subjects with coronary heart disease as compared to the other domains. Male gender was also more prevalent in subjects with peripheral artery disease as compared to renal insufficiency. Smoking was more prevalent in subjects with peripheral artery disease as compared to subjects with coronary heart disease.

Table 3 shows the risks of either having coronary heart disease, renal insufficiency or peripheral artery disease when having an elevated CRP level. An increased CRP level was associated with all domains of vascular disease, also after adjustment for age and gender. Adjustment for potential

| Table 4. Logistic regression analyses: microalbuminuria and its relative risk (odds ratio) on coronary heart disease, renal insufficiency and peripheral artery disease. |
|----------------------------------|-----------------|-----------------|-----------------|
|                                  | Coronary heart disease | Renal insufficiency | Peripheral artery disease |
| Model 1                          | 2.50 (1.90-3.29)    | 1.27 (0.80-2.00)  | 1.51 (1.09-2.10)   |
| Model 2                          | 1.81 (1.36-2.41)    | 1.10 (0.69-1.77)  | 1.22 (0.87-1.70)   |
| Model 3                          | 1.60 (1.17-2.18)    | 1.07 (0.65-1.77)  | 0.98 (0.68-1.41)   |

Figure 1. Interaction of C-reactive protein and age on the risk of vascular disease

Interactions between C-reactive protein and age on the risk of coronary heart disease (A), renal insufficiency (B) and peripheral artery disease (C).

confounders or risk modifiers, including the presence of microalbuminuria, yielded relative risks of CRP of approximately 1.5 for each domain of vascular disease. For microalbuminuria, a different pattern was seen (Table 4). Microalbuminuria was associated with an increased risk of having coronary or peripheral artery disease, whereas no relation with renal insufficiency was found. After adjustment for age and gender, and subsequent correction for risk factors as well as CRP, microalbuminuria was significantly associated with coronary heart disease only (OR 1.60 (1.17-2.18)).
Increased age and hypercholesterolemia were independently associated with all three domains of vascular disease, whereas male gender was independently related to coronary heart disease. Hypertension was independently associated with peripheral artery disease, whereas smoking was positively and obesity inversely related to renal insufficiency and peripheral artery disease.

We also investigated possible effect modification of CRP, microalbuminuria and CV risk factors on the risk of vascular disease. We found positive interactions only between age and CRP on the risk of coronary heart disease (Figure 1A, interaction $P<0.01$), renal insufficiency (Figure 1B, interaction $P<0.10$) and peripheral artery disease (Figure 1C, interaction $P=0.12$). The estimated increase in risk was at about 4-7 fold when both risk factors were present as compared to subjects without these risk markers. We did not find an interaction between CRP and microalbuminuria on either domain of vascular disease.

**Discussion**

In this study, we established that CRP and microalbuminuria are independent risk markers for vascular disease. Intriguingly, CRP and microalbuminuria each show a different risk profiling for the different vascular beds. Whereas CRP is important in heart, kidney and peripheral vasculature, microalbuminuria is associated only with coronary heart disease. Furthermore, the association of CRP with the risk for coronary heart disease, renal insufficiency and peripheral artery disease is mainly present in older subjects. Whether these cross-sectional conclusions can be extended to a future prediction of these vascular aberrations warrants a prospective study.

This study shows that CRP and microalbuminuria relate to vascular disease in different vascular beds independently of CV risk factors. Several studies have shown that CRP and albuminuria relate to the same risk factors for atherosclerotic CV disease, i.e. age, obesity, high blood pressure, smoking, the insulin resistance syndrome, dyslipidemia and other risk markers, even in non-diabetic or non-hypertensive populations. These risk factors however, could not explain the association between CRP, microalbuminuria and CV disease in our cohort, except for the association between microalbuminuria and peripheral artery disease, of which the latter was mainly accounted for by age. Furthermore, our study shows that CRP and microalbuminuria relate to vascular disease in different vascular beds independently of each other. Since CRP and microalbuminuria relate to various CV risk factors and concomitant atherosclerotic burden, a common link with respect to vascular disease is suggested in the literature. However, our data indicate that CRP and microalbuminuria may reflect different pathophysiological processes
leading to different types of vascular disease. In agreement with this suggestion, Stehouwer et al. showed that CRP and microalbuminuria independently predicted cardiovascular mortality in type 2 diabetic subjects. In addition, Jager et al. recently showed that CRP and microalbuminuria were independent risk markers for cardiovascular mortality in an age and glucose tolerance stratified sample of the population. Our data provide a substantiation of these findings with regard to vascular disease in different regions of the vasculature in non-diabetic subjects.

How can we explain that CRP is related to damage in all vascular beds, whereas microalbuminuria is preferentially related to the heart? It could be due to the fact that the sensitivity for CRP to detect vascular disease in subjects selected from the general population is higher than for microalbuminuria. It could also mean that in different regions of the vascular tree different risk factors play different roles, e.g. it has been suggested that smoking affects peripheral arteries more than the coronary arteries. The mechanism of the relation between CRP and progressive cardiovascular disease is assumed to be based on a low-grade inflammatory state either originating in the vasculature or a systemic effect on the vasculature due to inflammatory mediators released elsewhere in the body, e.g. adipose tissue, or due to external stimuli, e.g. smoking. Microalbuminuria is thought to reflect a generalised vascular leakiness due to vascular damage or (subclinical) atherosclerosis. Therefore, we did expect an equal contribution of CRP and microalbuminuria to vascular disease or a possible synergistic effect. The fact that microalbuminuria only relates to coronary heart disease may indicate that hemodynamics are important. This is the more likely as blood pressure is much more elevated in microalbuminuric subjects compared to subjects with an elevated CRP level (Table 1).

Interestingly, we found synergistic contributions of CRP and older age on the risk of coronary heart disease, renal insufficiency and peripheral artery disease. Thus, the effect of ageing on the risk of CV morbidity may well be mediated via the process of low-grade inflammation. In accordance with our data, the majority of other data available in the literature show consistent associations between CRP and CV disease in the elderly. To our knowledge, no other publications exist which describe an interaction between CRP and ageing on the risk of CV morbidity.

Our finding of the absence of an association between microalbuminuria and renal insufficiency seems somewhat contra-intuitive at first glance. Yet, our results are not discordant with the existing literature. In subjects with diabetes mellitus, for instance, it is well established that the early stage of disease is accompanied by an increase in glomerular filtration rate (GFR) – hyperfiltration – which is associated with the development of microalbuminuria. The GFR is elevated and remains so while microalbuminuria occurs. However, once macroalbuminuria ensues, renal function starts to decline. Our group has recently presented evidence for a comparable relationship between renal function and the urinary albumin excretion rate in the general, non-
diabetic, population. Like in subjects with diabetes mellitus, we found an association between microalbuminuria and high GFR, as well as an association between macroalbuminuria and low GFR.16

Our study has a number of limitations. First, it is cross-sectional in design and firm conclusions can only be drawn with a prospective follow-up of our cohort.

Second, the definitions of vascular disease are defined by clinical parameters: for coronary heart disease we used electrocardiograms and a questionnaire, for peripheral artery disease we used ankle brachial index and a questionnaire, and for renal insufficiency creatinine clearance was used. This possibly limits generalisation of the data to other populations and other types of vascular disease for example in cerebro.

Third, renal insufficiency was defined as a creatinine clearance of <60 ml/min which may have introduced biases. However, the results remained unchanged when we varied the criteria for the definition of renal insufficiency in the analysis (see methods).

Fourth, we used renal insufficiency as a parameter of vascular disease. Despite excluding subjects with known renal disease, some subjects could have a cause of the renal insufficiency other than generalised atherosclerosis or benign nephrosclerosis / glomerulosclerosis. However, since we also excluded subjects with leukocyturia and/or erythrocyturia, diabetes mellitus, and macroalbuminuria, it is unlikely that primary renal disease has contributed to the occurrence of low creatinine clearance. The importance of vascular disease in the renal domain, as a cause of mild renal insufficiency, is strongly corroborated by a recent study performed in the general population. In this study, it was not only shown that mild renal insufficiency is associated with cardiovascular mortality,31,32 but also that this association can be explained by co-occurrence of mild renal insufficiency with traditional cardiovascular risk factors.31 Furthermore, nephrosclerosis or glomerulosclerosis share similarities with generalised atherosclerosis and arteriolosclerosis.33,34 Thus, we feel that the use of renal insufficiency as parameter of vascular disease is valid.

Fifth, similar as subjects with macroalbuminuria, we also excluded subjects with CRP levels >10 mg/L suggestive of inflammatory processes other than the ‘atherosclerotic’ process. It has been suggested that, in the absence of infectious disease, CRP levels can be as high as up to 20 mg/L, especially in the elderly.35 We therefore also performed analyses in which we only excluded subjects with CRP levels >20 mg/L. This measure did not change the results of our study.

Finally, the risk estimates are moderate. However, the risks might be underestimated due to misclassification problems and, the relative risks of CRP and microalbuminuria on the three domains of vascular disease are comparable to that of other risk factors. Our analyses may therefore have underestimated the true association between CRP, microalbuminuria and the various domains of vascular disease.
In summary, our data show that CRP and microalbuminuria relate to several domains of vascular disease. However, an elevated CRP level independently relates to all three studied vascular disease parameters, i.e. heart, kidney and peripheral artery disease, whereas microalbuminuria was independently associated only with coronary heart disease. This indicates that CRP and microalbuminuria have different associations with vascular disease along the arterial tree. Potentially, both parameters should be independently used as predictors of CV morbidity. To date, it remains to be elucidated to what extent and by which mechanisms CRP and microalbuminuria are both related to macrovascular disease in non-diabetic subjects.
References


