Longitudinal Association of Glycemia and Microalbuminuria

The Framingham Offspring Study

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OBJECTIVE — To assess current and long-term associations of glycemia with microalbuminuria, a marker of generalized endothelial injury.

RESEARCH DESIGN AND METHODS — We measured clinical characteristics, fasting plasma glucose, and the urinary albumin-to-creatinine ratio (UACR) in 1,311 men and 1,518 women attending the sixth examination cycle (1995–1998) of the Framingham Offspring Study. After excluding participants with diabetes or cardiovascular disease (CVD) at the baseline examination (1971–1974), we used fasting glucose measured at baseline, examination 6, and at least two additional examinations from 1974 to 1995 in regression models to predict risk for microalbuminuria (UACR ≥30 mg/g) associated with baseline, current, and 24-year time-integrated glycemia.

RESULTS — Microalbuminuria was present in 9.5% of men and 13.4% of women. Among men, age-adjusted odds ratios (95% CI) for microalbuminuria associated with each 0.28 mmol/l (5 mg/dl) increase in baseline, current, and time-integrated glucose levels were 1.12 (1.00–1.16), 1.08 (1.05–1.10), and 1.16 (1.11–1.21), respectively. These effects persisted after adjustment for systolic blood pressure and other confounders. Higher glucose levels also predicted incident diabetes and CVD. Mean time-integrated glucose levels were highest among men who developed both CVD and microalbuminuria (SE 6.82 ± 0.16 mmol/l), intermediate among men with either condition (6.03 ± 0.65 mmol/l), and lowest among men with neither condition (5.49 ± 0.02 mmol/l, P < 0.001 for all pairwise comparisons). We observed similar associations in women.

CONCLUSIONS — Long-term hyperglycemia and subdiabetic glycemia increase risk for microalbuminuria. Microalbuminuria, type 2 diabetes, and CVD seem to arise together over the course of decades, consistent with the hypothesis that they share a common antecedent.

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Microalbuminuria, a mildly abnormal elevation in urinary albumin excretion, is a harbinger of progression to nephropathy in diabetes as well as a powerful predictor of cardiovascular disease (CVD) in both diabetic and nondiabetic subjects (1–3). Microalbuminuria is usually absent at diagnosis of type 1 diabetes but may be present at diagnosis of type 2 diabetes (4,5), partly because diagnosis is often delayed. Risk for microalbuminuria is proportional to the level and duration of hyperglycemia, with rates increasing within ~5 years of onset of diabetes (6–8). Aggressive glycemic control in diabetes prevents its onset and progression, demonstrating that hyperglycemia over the course of several years is a cause of microalbuminuria (9,10). However, temporal associations between subdiabetic glycemia and risk for microalbuminuria are not as well established.

Microalbuminuria also reflects diffuse vasculopathy and endothelial dysfunction, which in large arterial beds hypothetically leads to atherosclerosis and, in the microcirculation, may precede or contribute to development of insulin resistance and type 2 diabetes (11). The hypothesis that endothelial dysfunction is the “common soil” for the insulin resistance syndrome provides a plausible mechanism linking microalbuminuria, type 2 diabetes, and CVD (12,13). Several different studies suggest that the development of microalbuminuria, type 2 diabetes, insulin resistance, or CVD may each precede the development of the others, providing support for a common etiology (3,14–21).

If microalbuminuria is primarily caused by relatively recent hyperglycemia, then its development should be related to the recent onset of diagnosed diabetes. However, if microalbuminuria is also a marker of some “common soil,” then it should also be associated with subdiabetic levels of glycemia over many years before the development of type 2 diabetes or CVD. In this study, we exam-
ined the current and long-term associations of glycemia with risk for microalbuminuria, type 2 diabetes, and CVD among participants in a community-based cohort study.

RESEARCH DESIGN AND METHODS

Study subjects
Subjects were participants in the Framingham Offspring Study, a prospective observational study of risk factors for CVD (22). From 1995 through 1998, during the sixth quadrennial study cycle, 3,532 subjects underwent a standardized medical history, physical, and fasting laboratory examination including spot urine collection. Written informed consent was obtained before examination. Participants underwent similar evaluations (with the exception of urine collection) at the baseline study examination (1971–1974) and four subsequent examinations (1974–1995). In this analysis, we included participants who attended the baseline examination, the sixth examination, and at least two other examinations (a total of at least four of six examinations). After excluding 79 subjects with diabetes or CVD (both defined below) at the baseline examination, 127 attending three or fewer examinations, and 497 not providing a urine specimen at the sixth examination, a total of 2,829 subjects remained for analysis. Compared with included subjects, those excluded were older at the sixth examination (60 vs. 58 years, \( P < 0.0001 \)) and had higher fasting glucose levels (6.0 vs. 5.7 mmol/L, \( P = 0.0003 \)) but similar systolic blood pressure (129 vs. 128 mmHg, \( P = 0.1 \)). Of 79 subjects excluded due to baseline diabetes or CVD, 63 had urinary albumin-to-creatinine ratio (UACR) data at the sixth examination. The proportion with a UACR \( \geq 30 \) mg/g was significantly greater in these 63 subjects compared with the 2,829 study subjects (30.2 vs. 11.6%, \( P = 0.001 \)). Urinary albumin excretion was not assessed at the baseline or first several offspring examinations because its prognostic significance was not recognized at the time; therefore, we were unable to definitively exclude from the analysis subjects with microalbuminuria at baseline.

Exposure and outcome measurements
At each study visit, participants were examined after an 8-h overnight fast. Fasting glucose was measured in fresh plasma with a hexokinase reagent kit (A-gent glucose test; Abbott, South Pasadena, CA). Glucose assays were run in duplicate; intra-assay coefficients of variation were <3%. The primary exposures in this study were the baseline fasting glucose (examination 1, 1971–1974), the current fasting glucose (examination 6, 1995–1998), and the time-integrated fasting glucose (the mean of at least four of six values, 1971–1998). We classified subjects with diabetes at each examination if they reported hypoglycemic therapy or if the fasting glucose was \( \geq 7.0 \) mmol/L.

At each examination, the BMI was assessed as weight in kilograms divided by the square of height in meters (kg/m\(^2\)). Two blood pressure measurements were taken after subjects had been seated for at least 5 min; the averaged value was used. Participants reporting smoking at least one cigarette per day during the year before the examination were classified as current smokers. We assessed medication use for treatment of elevated blood pressure at each examination; current or past use of ACE inhibitors was assessed at examination 6. The fasting total plasma cholesterol and triglycerides were measured enzymatically, and the HDL cholesterol fraction was measured after precipitation of low-density and very-low-density lipoproteins with dextran sulfate-magnesium (23). CVD, including coronary heart disease (definite or probable myocardial infarction, angina pectoris, coronary insufficiency), cerebrovascular disease (embolic or hemorrhagic stroke, transient ischemic attack), and peripheral vascular disease (intermittent claudication), was ascertained at each examination using specific criteria described previously (24).

In addition, at examination 5 (1991–1994), we measured fasting insulin and HbA\(_{1c}\) levels. Insulin was measured in EDTA plasma as total immunoreactive insulin (Coat-A-Count Insulin; Diagnostic Products, Los Angeles, CA). Cross-reactivity of this assay with proinsulin at midcurve is \( \sim 40\% \), the intra-assay and interassay coefficients of variation ranged from 5.0 to 10.0%, and the lower limit of sensitivity was 8 pmol/L. HbA\(_{1c}\) was measured by high-performance liquid chromatography after an overnight dialysis against normal saline to remove the labile fraction. The mean (standard deviation) for this assay among nondiabetic subjects in this population was 5.22% (0.6) and the interassay and intra-assay coefficients of variation were <2.5%. The assay was standardized against the glycosylated hemoglobin assay used in the Diabetes Control and Complications Trial (9).

Prevalent albuminuria was assessed at examination 6 by the UACR from a single-void urine sample. The urine albumin concentration was measured by immunoturbidimetry (Tina-quant Albumin assay; Roche Diagnostics, Indianapolis, IN), and the urine creatinine concentration was determined using a modified Jaffe method. The UACR is a validated, reliable single-sample measure of urinary albumin excretion that is highly correlated with albumin excretion rates assessed by 24-h urine collection (25,26). We classified subjects with a UACR <30, 30–300, and >300 mg/g. The range of UACR in the latter group was 304–6,789 mg/g.

Statistical analysis
We analyzed data from men and women separately using \( \chi^2 \) tests to compare proportions among categories of albuminuria and multiple linear regression models to compare mean levels of baseline, current, and time-integrated fasting glucose among categories of albuminuria. We calculated the time-integrated fasting glucose level as the arithmetic mean of values obtained at four or more examinations and the rate of change of fasting glucose over time as the difference between current and baseline levels. We used logistic regression models, with adjustment for age, to test for associations between fasting glucose levels and albuminuria. In logistic regression models and for analyses stratified by diabetes or CVD, we grouped all subjects with a UACR \( \geq 30 \) mg/g (because few subjects had a UACR >300 mg/g); we refer to the group with UACR \( \geq 30 \) mg/g as having microalbuminuria. We also performed logistic regression analyses excluding subjects with UACR >300 mg/g; because findings were similar, we only show results of analyses including all subjects with UACR \( \geq 30 \) mg/g. Additional logistic regression models were used to control for effects of age, baseline, current, or time-integrated systolic blood pressure, BMI and lipid levels, current smoking and antihypertensive medica-
tion use at each examination, and ACE inhibitor use at or before examination 6. We further stratified analyses by no diabetes or incident diabetes and no CVD or incident CVD as of examination 6. In additional logistic regression models, we tested for associations between fasting glucose levels and risk for diabetes or CVD. We used SAS software for statistical analyses and defined statistical significance as \( P < 0.05 \) (27).

**RESULTS** — Among 1,311 men, 1.6% had a UACR >300 mg/g and 7.9% had a UACR 30–300 mg/g; among 1,518 women, 0.8% had a UACR >300 mg/g and 12.6% had a UACR 30–300 mg/g. Age-adjusted mean fasting glucose levels at each examination according to UACR levels at examination 6 are shown in Fig. 1 (top panels), and corresponding mean (±
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**Longitudinal association of glycemia and albuminuria**

Table 1—Mean levels of fasting plasma glucose by category of UACR

<table>
<thead>
<tr>
<th>UACR</th>
<th>Number of subjects</th>
<th>Age at examination 6 (1995–1998)</th>
<th>Fasting plasma glucose (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 mg/g</td>
<td>1,186</td>
<td>57.8 (0.3)</td>
<td>5.7 (0.01)</td>
</tr>
<tr>
<td>30–300 mg/g</td>
<td>104</td>
<td>65.0 (0.9)</td>
<td>5.8 (0.05)</td>
</tr>
<tr>
<td>&gt;300 mg/g</td>
<td>21</td>
<td>63.7 (2.1)*</td>
<td>6.0 (0.1)*</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 mg/g</td>
<td>1,315</td>
<td>57.9 (0.3)</td>
<td>5.4 (0.01)</td>
</tr>
<tr>
<td>30–300 mg/g</td>
<td>191</td>
<td>62.0 (0.7)</td>
<td>5.5 (0.03)</td>
</tr>
<tr>
<td>&gt;300 mg/g</td>
<td>12</td>
<td>65.1 (2.8)*</td>
<td>5.6 (0.1)*</td>
</tr>
</tbody>
</table>

Data are age-adjusted mean (SE), time-integrated values are the mean of 4+ examinations, and slopes are differences between the examination 6 and examination 1 fasting plasma glucose levels. UACRs were measured at examination 6. *P = 0.0001 for trend across UACR categories; †P = 0.01; ‡P = 0.02

SE age, baseline, current, and time-integrated fasting glucose levels and the rate of change of fasting glucose over 24 years are shown in Table 1. Among both men and women, those with a UACR ≥30 mg/g had significantly higher fasting glucose levels at baseline and at every subsequent examination compared with those who had normal urinary albumin excretion. Subjects with a UACR >300 mg/g had even higher fasting glucose levels over time than those with lesser degrees of urinary albumin excretion. For instance, among 1,186 men with normal urinary albumin excretion, the time-integrated fasting glucose level was 5.5 mmol/l; among 104 men with a UACR 30–300 mg/g, the time-integrated fasting glucose level was 6.0 mmol/l; and among 21 men with a UACR >300 mg/g, it was 7.0 mmol/l (P = 0.0001 for trend).

Mean levels of HbA1c at examination 5, a time-integrated measure of average glycemia over the preceding 2–3 months, also increased with increasing UACR. Among men with a normal UACR, the mean (SE) HbA1c was 5.4% (0.03); among those with a UACR 30–300 mg/g, it was 5.7% (0.1); and among those with a UACR >300 mg/g, it was 6.8% (0.2) (P = 0.0001 for trend). Among women with a normal UACR, the mean HbA1c was 5.3% (0.03); among those with a UACR 30–300 mg/g, it was 5.6% (0.1); and among those with a UACR >300 mg/g, it was 7.0% (0.3) (P = 0.0001 for trend).

Mean levels of fasting insulin at examination 5, a marker of insulin resistance, also increased with increasing UACR. Among men with a normal UACR, the geometric mean (SE) fasting insulin was 179 (6.1); among those with a UACR 30–300 mg/g, it was 210 pmol/l (6.2); and among those with a UACR >300 mg/g, it was 209 pmol/l (6.5) (P = 0.0001 for trend). Among women with a normal UACR, the mean fasting insulin was 162 pmol/l (6.1); among those with a UACR 30–300 mg/g, it was 176 pmol/l (6.1); and among those with a UACR >300 mg/g, it was 229 pmol/l (6.6) (P = 0.0001 for trend).

Associations of fasting glucose with microalbuminuria (UACR ≥30 mg/g) as compared with normoalbuminuria (UACR <30 mg/g), adjusted for age and confounding factors, are shown in Table 2. Even after adjustment, current and time-integrated fasting glucose levels remained significantly associated with microalbuminuria, but associations with baseline fasting glucose levels were attenuated. For instance, among men, the age-adjusted odds ratio for microalbuminuria associated with a 0.28-mmol/l (5 mg/dl) increase in the baseline fasting glucose level was 1.12 (95% CI 1.00–1.26), and for a similar increase in the time-integrated fasting glucose was 1.16 (1.11–1.21). Further adjustment for baseline systolic blood pressure weak-

Table 2—Odds ratios for microalbuminuria per 0.28-mmol/l increase in baseline, current, or time-integrated fasting plasma glucose levels

<table>
<thead>
<tr>
<th></th>
<th>Baseline fasting glucose</th>
<th>Current fasting glucose</th>
<th>Time-integrated glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age-adjusted</td>
<td>Age- and SBP-adjusted</td>
<td>Multivariable-adjusted*</td>
</tr>
<tr>
<td>Men</td>
<td>1.12 (1.00–1.26)</td>
<td>1.07 (0.95–1.21)</td>
<td>1.06 (0.94–1.20)</td>
</tr>
<tr>
<td></td>
<td>P = 0.05</td>
<td>P = 0.03</td>
<td>P = 0.3</td>
</tr>
<tr>
<td>Women</td>
<td>1.11 (1.01–1.22)</td>
<td>1.09 (0.99–1.20)</td>
<td>1.10 (0.99–1.21)</td>
</tr>
<tr>
<td></td>
<td>P = 0.03</td>
<td>P = 0.07</td>
<td>P = 0.07</td>
</tr>
<tr>
<td>Men</td>
<td>1.08 (1.05–1.10)</td>
<td>1.06 (1.03–1.09)</td>
<td>1.07 (1.01–1.10)</td>
</tr>
<tr>
<td></td>
<td>P = 0.0001</td>
<td>P = 0.0001</td>
<td>P = 0.0001</td>
</tr>
<tr>
<td>Women</td>
<td>1.07 (1.05–1.10)</td>
<td>1.07 (1.04–1.09)</td>
<td>1.07 (1.04–1.10)</td>
</tr>
<tr>
<td></td>
<td>P = 0.0001</td>
<td>P = 0.0001</td>
<td>P = 0.0001</td>
</tr>
<tr>
<td>Men</td>
<td>1.16 (1.11–1.21)</td>
<td>1.14 (1.09–1.20)</td>
<td>1.13 (1.07–1.18)</td>
</tr>
<tr>
<td></td>
<td>P = 0.0001</td>
<td>P = 0.0001</td>
<td>P = 0.0001</td>
</tr>
<tr>
<td>Women</td>
<td>1.14 (1.09–1.19)</td>
<td>1.12 (1.07–1.17)</td>
<td>1.14 (1.09–1.20)</td>
</tr>
<tr>
<td></td>
<td>P = 0.0001</td>
<td>P = 0.0001</td>
<td>P = 0.0001</td>
</tr>
</tbody>
</table>

Data are odds ratios (95% CI) associated with a 0.28 mmol/l (5 mg/dl) increase in the fasting glucose level. Microalbuminuria is defined as a UACR ≥30 mg/g measured at examination 6. *Model is adjusted for age, systolic blood pressure (SBP), BMI, smoking, ACE inhibitor use, other drug therapy for hypertension, total cholesterol, HDL cholesterol, and triglycerides.
ened associations between baseline fasting glucose and microalbuminuria (among men: odds ratio 1.07, 95% CI 0.95–1.21), but further adjustment for time-integrated systolic blood pressure did not substantially attenuate the association between time-integrated fasting glucose and microalbuminuria (among men: 1.14, 1.09–1.20). Additional adjustment for BMI, lipid levels, cigarette smoking, and use of antihypertensive and ACE inhibitor medications did not further alter these relationships.

We also assessed interrelationships between time-integrated glycemia, microalbuminuria, and development of type 2 diabetes or CVD. Between the baseline examination and examination 6, type 2 diabetes developed in 134 men (10.2%) and in 111 women (7.3%). The mean duration of diabetes was 6.6 years; 32.5% of subjects had diabetes for 0–3 years, 25.9% had diabetes for 4–7 years, 18.0% had diabetes for 8–11 years, and 23.7% had diabetes for 12–18 years. Development of diabetes was strongly associated with microalbuminuria: 29.9% of men with diabetes had microalbuminuria compared with 7.2% of men without diabetes (P = 0.001), and 35.1% of women with diabetes had microalbuminuria compared with 11.7% of women without diabetes (P = 0.001). Time-integrated glycemia also predicted development of diabetes: the age-adjusted odds ratio for incident diabetes associated with a 0.28-mmol/l (5-mg/dl) increase in time-integrated fasting glucose was 1.14 (95% CI 1.08–1.20) among men and 1.10 (1.03–1.18) among women. These relationships are shown in Fig. 1 (middle panels). Subjects with the highest fasting glucose levels over time were those in whom CVD and microalbuminuria developed (time-integrated mean ± SE fasting glucose 6.82 ± 0.16 mmol/l in men and 6.63 ± 0.26 mmol/l in women), whereas those with either CVD or microalbuminuria had intermediate fasting glucose levels over time (6.03 ± 0.65 mmol/l in men and 5.70 ± 0.05 mmol/l in women), and those with neither condition had the lowest levels (5.49 ± 0.02 mmol/l in men and 5.22 ± 0.02 mmol/l in women; P < 0.001 for pairwise comparisons among categories in both sexes). Among men and women with or without CVD, elevated levels of time-integrated fasting glucose were significantly associated with prevalent microalbuminuria. Likewise, proportions of subjects with microalbuminuria among those in whom both diabetes and CVD developed were significantly higher compared with those in whom neither condition developed (among men, 56.5 vs. 6.7%; P = 0.001; among women, 44.4 vs. 11.6%).

**CONCLUSIONS** — Hyperglycemia in the diabetic range can cause microalbuminuria. Controlled trials demonstrate that intensive lowering of blood glucose toward normal levels in patients with diabetes prevents the onset and progression of microalbuminuria, with a continuous graded relationship between level of glycemia and risk of abnormal urinary albumin excretion (6,9,10). Mechanisms of glucose-related albuminuria include glycation of basement membrane proteins with loss of charge selectivity andglomerular hyperperfusion and hyperfiltration (28–30). The clinical course of abnormal urinary albumin excretion in patients with diabetes is quite heterogeneous; 11–67% of patients progress to overt proteinuria over 5–15 years of follow-up (1,31,32). Heterogeneity in progression of albuminuria is determined (in addition to variation in glycemia) by baseline urinary albumin excretion rate, cigarette smoking, levels of blood pressure and serum lipids, and genetic effects (29,33–36).

Our study confirms that current and antecedent elevations in fasting plasma glucose are strongly associated with abnormal urinary albumin excretion. We found that 30–35% of Framingham subjects with type 2 diabetes of a few months’ to ≥18 years’ duration had microalbuminuria, similar to published microalbuminuria prevalence rates of 17% in newly diagnosed type 2 diabetes (5) and 22–32% in established older onset diabetes (7,37). An important novel finding of our study is that risk for microalbuminuria associated with hyperglycemia was detectable up to at least 24 years before assessment of urinary albumin excretion. Elevations in baseline and 24-year time-integrated fasting glucose were strongly associated with microalbuminuria; subjects in whom type 2 diabetes developed over 24 years were also those most likely to have prevalent microalbuminuria. These associations were similar for men and women and, for time-integrated glycemia, were independent of age, elevated systolic blood pressure, and other confounding factors.

Risk for microalbuminuria was not, however, limited to diabetic levels of fasting glucose. Another important novel finding is that subtle elevations in apparently normal levels of time-integrated fasting glucose increased risk of microalbuminuria. Some prior data suggest an association between subdiabetic glucose intolerance and microalbuminuria (8,38); however, the long-term nature of this relationship has not previously been observed. Even modest elevations in levels of HbA1c, measured 4 years before assessment of microalbuminuria, increased risk. The associations we found between baseline, time-integrated, and current levels of fasting glucose and microalbuminuria suggest that risk for microalbuminuria, like risk for CVD, may increase in a graded fashion across the spectrum of glucose tolerance (39). We defined microalbuminuria using cutpoints based on risk of progression to nephropathy in patients with diabetes; in nondiabetic subjects, lower thresholds for urinary
albumin excretion are associated with increased risk of CVD (3,21). Further work is required to determine whether there is any glycemic threshold below which there is no risk for increased urinary albumin excretion or CVD.

Our data show that subjects with microalbuminuria were those most likely to have developed not only type 2 diabetes but also CVD over the antecedent 24 years of observation. Considered another way, higher levels of time-integrated fasting glucose increased risk not just of type 2 diabetes, but also of CVD and microalbuminuria. Time-integrated fasting glucose levels were highest among subjects with both CVD and microalbuminuria, intermediate among those with either CVD or microalbuminuria, and lowest among those without either condition. We also found a positive association between levels of fasting insulin at examination 5 (a marker of insulin resistance) and abnormal urinary albumin excretion. Our data suggest that type 2 diabetes, CVD, and microalbuminuria arose together over the course of decades; these long-term associations are consistent with the hypothesis that they may be caused by a common pathogenic antecedent, putatively insulin resistance or endothelial dysfunction (12,13). Microalbuminuria is a marker of diffuse endothelial dysfunction associated with widespread vascular abnormalities, including impaired arterial reactivity and elevated levels of markers of endothelial activation (40,41). Several previous studies suggest that microalbuminuria, type 2 diabetes, insulin resistance, or CVD may each arise from one another over the course of 4–8 years (3.14–20). Our data suggest that these associations may be traceable over a longer period of time, although it is difficult to pinpoint exactly when their relationship begins.

There is evidence for a genetic basis for the insulin-resistant phenotype (42); insulin resistance may also be programmed in utero (43), with persistent effects apparent through childhood (44).

Certain limitations of our data influence its interpretation. We lack baseline measurement of urinary albumin excretion and could not definitively exclude subjects with baseline microalbuminuria, as we did for baseline diabetes and CVD. However, we probably excluded many with baseline microalbuminuria by excluding subjects with baseline diabetes and CVD, given strong cross-sectional relationships between microalbuminuria, diabetes, and CVD: subjects with baseline diabetes and CVD or those in whom incident diabetes and CVD developed were more than three times more likely to have microalbuminuria than those with neither condition. Therefore, microalbuminuria in this study probably represents many incident cases. Also, we assessed urinary albumin excretion on the basis of a single measurement. Although UACR is a good single-sample marker of elevated urinary albumin excretion, it is associated with enough intra-individual variability that some cases may be misclassified, resulting in an underestimate of associations between microalbuminuria and hyperglycemia.

In conclusion, we found a strong association between abnormal urinary albumin excretion and levels of fasting glucose measured over the antecedent 24 years. This association was apparent, even within the normal range of fasting glucose, and was independent of systolic blood pressure and other risk factors for microalbuminuria. Although diabetic hyperglycemia can cause microalbuminuria, mutual associations over two decades among diabetic and subdiabetic hyperglycemia, CVD, and microalbuminuria also provide evidence of a common pathogenic antecedent. If this “common soil” is insulin resistance, then our findings have preventive implications. Long-term associations between metabolic risk factors strongly suggest that interventions to reduce insulin resistance and risk for diabetes and CVD should begin in childhood and extend well into adult life.

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References