Microalbuminuria is strongly associated with NIDDM and hypertension, but not with the insulin resistance syndrome: the Hoorn Study

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Summary Microalbuminuria is a strong predictor of cardiovascular disease. The aim of this study was to investigate whether microalbuminuria is part of a cluster of risk factors, the insulin resistance syndrome (IRS), or whether it is only associated with, and presumably a complication of, hypertension and non-insulin-dependent diabetes mellitus (NIDDM). An age-, sex- and glucose tolerance-stratified random sample from a 50–75 year old general population ($n = 622$) was investigated. The urinary albumin-to-creatinine ratio was measured in an early morning spot urine sample. Microalbuminuria was defined as an albumin-to-creatinine ratio greater than 2.0 mg/mmol. We considered, as IRS-related variables, fasting hyperinsulinaemia, insulin resistance (IR; calculated from the formula of the homeostasis model assessment), dyslipidaemia, glucose intolerance, hypertension and waist-to-hip ratio (WHR). Dyslipidaemia was defined as levels of HDL-cholesterol in the lowest and / or levels of triglyceride in the highest tertile. Fasting insulin levels, IR and WHR were divided into tertiles; the highest tertiles were compared to the lowest tertiles. Age-, sex- and glucose tolerance-adjusted analyses showed microalbuminuria to be significantly associated with hypertension, NIDDM and WHR. In multiple logistic regression analyses, microalbuminuria showed independent associations with hypertension, NIDDM and WHR, with odds ratios (ORs [95 % confidence interval]) of 3.33 (1.86–5.96), 2.26 (1.14–4.48) and 2.49 (1.09–5.70), respectively. No associations were found with impaired glucose tolerance, hyperinsulinaemia, IR or dyslipidaemia. Multiple logistic regression analyses in diabetic and non-diabetic subjects separately showed that microalbuminuria was independently associated only with hypertension (ORs 4.31 and 2.69). In this Caucasian population, microalbuminuria was associated with hypertension, NIDDM and WHR and not with other variables of the IRS. It is therefore likely that microalbuminuria is a complication of hypertension and NIDDM, and not an integral part of the IRS. [Diabetologia (1998) 41: 694–700]

Keywords Microalbuminuria, insulin resistance syndrome, non-diabetic subjects, non-insulin-dependent diabetes mellitus, hypertension, population.

Microalbuminuria (MA) is associated with an increased risk of cardiovascular disease in non-insulin-dependent diabetes mellitus (NIDDM) [1–3], as well as in the apparently healthy middle-aged and elderly general population [4, 5]. It has been proposed that MA belongs to a cluster of risk factors known as the insulin resistance syndrome (IRS), which implies that MA would be closely associated not only with hypertension [6–9] and NIDDM [10, 11], but also with impaired glucose tolerance (IGT) [10], obesity [12, 13], insulin resistance (IR) [6, 8, 9, 11, 14], hyperinsulinaemia [15, 16] and dyslipidaemia [6, 16, 17].

These associations might then explain the association between MA and the increased risk of cardiovascular disease [6–11, 14–18]. Alternatively, MA may be a complication of hypertension and NIDDM, possibly reflecting endothelial dysfunction [19, 20], without having associations with other components of the IRS [21–23]. The latter hypothesis, if correct, implies that MA cannot be used as a marker for the IRS in the general population.

Previous experimental [6, 8, 9, 11, 14, 17, 22] and epidemiological [7, 10, 15, 16, 18, 21, 23] investigations of the link between MA and the IRS have yielded conflicting results. These studies have, however, been limited by not being population-based [6–9, 11, 18, 21, 22], by including only part of the spectrum of glucose tolerance and the IRS [6–11, 14, 16, 17, 21, 23], and / or by not being ethnically homogeneous [10, 18, 23]. The latter is important, because the prevalence and the pathogenesis of MA may differ according to ethnicity. For example, non-Caucasian populations showed higher prevalences of MA than Caucasian populations, both among subjects with NIDDM [23–25] as well as among non-diabetic subjects [16, 18, 25]. In view of these considerations, we decided to study the association between MA and the IRS in a population-based, sex-, age- and glucose tolerance- stratified sample of an ethnically homogeneous, Caucasian population.

Subjects and methods

Subjects. The Hoorn Study is a cross-sectional survey of glucose intolerance and related complications in 2484 randomly selected Caucasian men and women aged 50–75 years as described in detail elsewhere [26]. Of this population, an age-, sex- and glucose tolerance-stratified sample of 680 subjects (279 with normal glucose tolerance [NGT], 219 with IGT and 182 with NIDDM [27]; based on one oral glucose tolerance test [OGTT]); 95.5% of those invited underwent a second OGTT (except those subjects with previously diagnosed NIDDM treated with oral blood glucose-lowering agents or insulin, $n = 67$ [26]) and were asked to collect urine for measurement of the albumin-to-creatinine ratio (see below). The final definition of glucose tolerance was based on the mean of the two OGTTs (314 NGT, 192 IGT and 174 NIDDM subjects [27]). All participants gave their informed consent for these studies, which were approved by the local ethics committee.

Methods. Blood pressure, weight and height were measured and body mass index and waist-to-hip ratio (WHR) were calculated as previously described [26]. Information on smoking habits and protein intake was obtained by a self-administered questionnaire. We measured fasting and 2-h post-load venous plasma glucose levels, HbA_{1c}, fasting plasma levels of insulin (with a specific assay) and proinsulin, and fasting serum levels of total cholesterol, HDL cholesterol and triglycerides, as described in detail elsewhere [26, 28]. Fasting proinsulin levels were not measured in previously diagnosed NIDDM ($n = 67$). The Friedewald formula was used to calculate the LDL cholesterol concentration, except when serum triglyceride was greater than 8.0 mmol/l ($n = 3$) [29].

An early morning first voided spot urine sample was collected. The presence of leukocytes was tested by microscopy and scored as positive (> 5 leukocytes per high powerfield) or negative. Urinary albumin was measured by rate nephelometry (Array Protein System, Beckman, Galway, Ireland) with a threshold of 6.2 mg/l and intra- and inter-assay coefficients of variation of 5% and 8%, respectively. Urinary creatinine was measured by a modified Jaffé method. The urinary albumin-to-creatinine ratio (ACR) was calculated; ACR ≤ 2.0 mg/mmol was defined as normoalbuminuria and ACR above 2.0 mg/mmol as microalbuminuria. (An overnight ACR > 2.0 mg/mmol predicts an albumin excretion rate > 30 μg/min with a high sensitivity and specificity [30].) The reproducibility of the ACR was calculated from a representative sample of 185 subjects who collected a second urine sample in similar fashion. The Kappa coefficient of the ACRs in these subjects was 0.59, indicating moderate agreement [31]. The analyses were performed on 622 subjects of the initial 680; 24 urine samples were lost and 34 subjects used angiotensin converting enzyme inhibitors and were therefore excluded. For 174 subjects the ACR was based on the mean of two measurements. Six subjects had an ACR above 30 mg/mmol, a level which approximates an albumin excretion of 300 mg/24 h, i.e. the upper limit for microalbuminuria. Excluding these subjects from the analyses did not materially affect any of the results, which are therefore presented for the entire group.

Statistical analysis. All analyses were performed with the Statistical Package for the Social Sciences (SPSS). We postulated that if MA was part of the IRS, MA should be related not only to hypertension and NIDDM (of which MA may be a complication, as suggested by the alternative hypothesis described above), but also to dyslipidaemia, central obesity and hyperinsulinaemia or IR. Therefore, multiple logistic regression analyses were performed to investigate the association between the presence of MA and IRS-related variables. The Wald test was used to test significance. All odds ratios for MA were adjusted for age, sex and glucose tolerance. We used three different models, in which each separate variable was adjusted for the other IRS-related variables. In the first, we considered, as IRS-related variables, fasting hyperinsulinaemia, dyslipidaemia, glucose intolerance (i.e. IGT or NIDDM), hypertension and WHR [32, 33]. In the second, fasting hyperinsulinaemia was replaced by IR, according to the formula of the homeostasis model assessment: IR = fasting insulin × fasting glucose / 22.4 [34]. (We chose fasting rather than post-glucose insulin levels as an estimate of IR, because fasting but not post-glucose insulin levels have been shown to correlate closely with insulin-mediated glucose uptake in both NGT and NIDDM [35].) In the third model, fasting hyperproinsulinaemia, another possible marker of IR [36], replaced fasting hyperinsulinaemia. Hypertension was defined as diastolic blood pressure over 95 mmHg and / or systolic blood pressure over 160 mmHg and / or the use of antihypertensive drugs. Dyslipidaemia was defined as levels of HDL-cholesterol in the lowest and / or triglycerides in the highest tertile. Fasting insulin levels, IR and WHR (separate per sex) were divided into tertiles; the highest tertiles were compared to the lowest.

Finally, to investigate as thoroughly as possible the putative association of MA with the IRS, we created two 'sum' Z-scores for each subject. For each IRS-related variable a Z-score ((value(×) – mean(×)) / sd(×)) was calculated. The first 'sum' Z-score was the sum of the Z-scores of the continuous variables reflecting NIDDM and hypertension, i.e. fasting glucose level and systolic and diastolic blood pressure. The second 'sum' Z-score was the sum of Z-scores of the other IRS-related variables, i.e. fasting levels of insulin, triglycerides and HDL-cho-
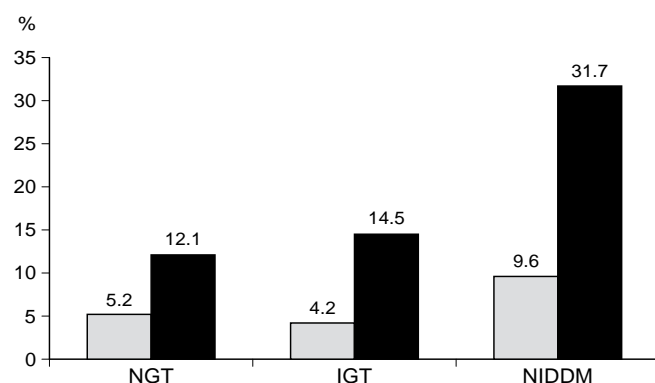
Fig. 1. Age-standardized prevalence of microalbuminuria in different glucose tolerance groups with or without hypertension, ▨ = normotensive subjects, ■ = hypertensive subjects, NGT = normal glucose tolerance, IGT = impaired glucose tolerance, NIDDM = non-insulin-dependent diabetes mellitus.

lesterol, and WHR, a higher Z-score indicating a more unfavourable spectrum. The idea of this analysis is that weak associations between MA and these other IRS-related variables might reveal themselves when considered in combination, even if each of these associations were too weak to be significant by themselves. Thus, to investigate whether higher 'sum' Z-scores were associated with a higher risk of MA, we calculated the prevalence of MA in all combinations of tertiles of the two 'sum' Z-scores.

Results

The prevalence of MA in this sample was 10.9 % (68/622) and was higher among diabetic than among non-diabetic subjects (21.3 vs 7.5 %) and among hypertensive than among non-hypertensive subjects (20.1 vs 5.8 %; Fig. 1). The prevalence of MA, in the general 50–75-year-old Caucasian population of Hoorn, age-standardized to the age distribution in the general population and calculated by direct standardisation, was 8.2 % (22.6 % and 6.9 % among dia-

Table 1. Baseline characteristics of subjects with normo- and microalbuminuria

	Normal glucose tolerance subjects		Impaired glucose tolerance subjects		Diabetic subjects	
	ACR ≤ 2.0 mg/mmol	ACR > 2.0 mg/mmol	ACR ≤ 2.0 mg/mmol	ACR > 2.0 mg/mmol	ACR ≤ 2.0 mg/mmol	ACR > 2.0 mg/mmol
n	275	20	157	15	122	33
Sex (% male)	50	65	45	53	46	33
Age (years)	63 ± 7	68 ± 6	65 ± 7	65 ± 7	66 ± 7	67 ± 6
Fasting glucose (mmol/l)	5.4 (5.1–5.7)[a]	5.5 (5.1–5.8)[a]	5.9 (5.5–6.6)[a]	6.0 (5.9–6.4)[a]	7.5 (6.4–8.5)[a]	7.0 (6.1–8.4)[a]
HbA$_{1c}$ (% of haemoglobin)	5.4 ± 0.5	5.2 ± 0.5	5.6 ± 0.5	5.6 ± 0.4	7.0 ± 1.9	8.0 ± 1.7
Fasting insulin (pmol/l)	79 (60–97)[a]	80 (66–110)[a]	93 (72–126)[a]	79 (65–151)[a]	116 (83–162)[a]	131 (82–168)[a]
Hyperinsulinaemia (%)[b]	18	30	41	40	55	58
Insulin resistance (pmol · mmol · l^{-2})[c]	19 (14–23)[a]	20 (16–26)[a]	25 (18–34)[a]	20 (18–46)[a]	38 (26–57)[a]	44 (31–66)[a]
Insulin resistance (%)[d]	8	5	36	47	74	82
Fasting proinsulin (pmol/l)	9 (5–14)[a]	13 (7–19)[a]	13 (8–21)[a]	16 (9–24)[a]	22 (12–31)[a]	23 (9–42)[a]
Body mass index (kg/m^2)	26.0 ± 3.4	26.9 ± 3.6	27.9 ± 4.0	27.1 ± 3.8	28.2 ± 4.1	29.7 ± 5.4
Waist-to-hip ratio (female)	0.83 ± 0.07	0.88 ± 0.06	0.88 ± 0.07	0.87 ± 0.07	0.91 ± 0.08	0.94 ± 0.05
Waist-to-hip ratio (male)	0.94 ± 0.06	0.99 ± 0.06	0.98 ± 0.06	0.96 ± 0.06	0.99 ± 0.08	0.99 ± 0.06
Total cholesterol (mmol/l)	6.7 ± 1.1	6.1 ± 1.0	6.8 ± 1.3	6.7 ± 1.3	6.4 ± 1.3	6.6 ± 1.3
LDL-cholesterol (mmol/l)	4.6 ± 1.0	4.2 ± 0.9	4.7 ± 1.1	4.5 ± 1.1	4.2 ± 1.1	4.2 ± 1.1
HDL-cholesterol (mmol/l)	1.4 ± 0.4	1.3 ± 0.4	1.3 ± 0.3	1.2 ± 0.3	1.1 ± 0.3	1.1 ± 0.3
Triglycerides (mmol/l)	1.4 (1.1–1.9)[a]	1.2 (0.8–1.4)[a]	1.6 (1.2–2.2)[a]	2.4 (1.6–2.9)[a]	1.9 (1.3–2.7)[a]	1.5 (1.2–4.4)[a]
Diastolic blood pressure (mmHg)	81 ± 10	81 ± 10	83 ± 9	93 ± 13	82 ± 10	84 ± 13
Systolic blood pressure (mmHg)	133 ± 18	137 ± 20	141 ± 17	156 ± 28	140 ± 18	153 ± 19
Hypertension (%)[e]	21	40	42	73	46	79
Current smokers (%)	30	25	22	13	24	24
Ex-smokers (%)	34	50	36	53	34	39

Data are mean ± standard deviation unless otherwise indicated. [a] median (25–75 th percentiles); [b] percentage of subjects with fasting insulin levels in the highest tertile in the whole sample (> 101 pmol/l); [c] HOMA = fasting insulin × fasting glucose/22.4; [d] percentages of subjects with IR in the highest ter-

tile in the whole sample (> 29.8 pmol · mmol · l^{-2}); [e] Hypertension is defined as diastolic blood pressure > 95 mmHg and/or systolic blood pressure > 160 mmHg and/or the use of antihypertensive drugs

Table 2. Age-, sex- and glucose tolerance-adjusted odds ratios (95 % confidence intervals) for microalbuminuria of insulin resistance syndrome-related variables

	All subjects (n = 622)	Non-diabetic subjects (n = 467)	Diabetic subjects (n = 155)
Hypertension	3.29 (1.86–5.82)	2.72 (1.31–5.67)	3.99 (1.56–10.22)
NIDDM[a]	3.35 (1.83–6.12)		
Impaired glucose tolerance[b]	1.21 (0.60–2.45)	1.24 (0.61–2.51)	
Dyslipidaemia[c]	1.14 (0.66–1.96)	1.06 (0.50–2.23)	1.07 (0.47–2.44)
Waist-to-hip ratio[d, e]	2.41 (1.10–5.29)	2.49 (1.02–6.05)	3.67 (0.45–30.15)
Fasting hyperinsulinaemia[f]	1.39 (0.68–2.84)	1.56 (0.61–4.00)	0.93 (0.30–2.89)
Insulin resistance[g]	1.84 (0.78–4.36)	1.45 (0.51–4.15)	1.96 (0.23–16.86)
Fasting hyperproinsulinaemia[h,i]	1.62 (0.65–4.01)	2.33 (0.84–6.46)	0.30 (0.04–2.06)

[a] compared to subjects with normal glucose tolerance; [b] compared to subjects with normal glucose tolerance; [c] defined as HDL-cholesterol in the lowest and/or triglycerides levels in the highest tertile; [d] the highest compared to the lowest tertile of waist-to-hip ratio per sex; [e] associations with BMI were weaker; [f] highest (> 101 pmol/l) compared to the lowest tertile of fasting insulin levels; [g] according to the HOMA-formula (= fasting insulin × fasting glucose/22.4), comparing the highest (> 29.8 pmol · mmol · l^{-2}) with the lowest tertile of insulin resistance; [h] the highest (> 15.7 pmol/l) compared to the lowest tertile of fasting proinsulin levels; [i] obtained in all subjects except for the previously known diabetic subjects

betic and non-diabetic subjects, 16.4 % and 5.9 % among hypertensive and non-hypertensive subjects, and 5.4 % among normotensive non-diabetic subjects).

Among NGT subjects, those with MA were older and had higher WHR and systolic blood pressure than did those with normoalbuminuria. Among diabetic subjects, HbA$_{1c}$ and systolic blood pressure were higher in the micro- than in the normoalbuminuric subjects. Thirty-eight percent of the diabetic subjects were previously known diabetic subjects. The IR and fasting insulin levels were similar between newly detected and previously known diabetic subjects (data not shown). Among NGT, IGT and NIDDM subjects, the prevalence of hypertension was higher among those with compared to those without MA (Table 1).

Age-, sex- and glucose tolerance-adjusted analyses showed MA to be significantly associated with hypertension, NIDDM and WHR (Table 2). MA was associated with hypertension and WHR in the non-diabetic subjects and with hypertension among diabetic subjects. Analyses of NGT and IGT subjects separately showed MA to be associated with hypertension and WHR but not with the other IRS-related variables (data not shown). As a consequence of the low prevalence of MA among NGT and IGT subjects (20/295 and 15/172, respectively), these analyses were unstable.

To further investigate the association between MA and IRS-related variables, multiple logistic regression analyses were performed with age, sex, NIDDM, IGT, hypertension, fasting hyperinsulinaemia, dyslipidaemia and WHR as independent variables. MA was significantly associated with NIDDM, hypertension and WHR. Analyses of the non-diabetic and the diabetic subjects separately showed similar results (Table 3), as did multiple regression analyses with IR or hyperproinsulinaemia replacing hyperinsulinaemia (i.e. the second and third model referred to in the

Table 3. Multiple logistic regression analyses with microalbuminuria as dependent variable and insulin resistance syndrome-related variables as independent variables

	OR (95 % CI)	p-value
All subjects (n = 622)		
Non-insulin-dependent diabetes mellitus	2.26 (1.14–4.48)	0.02
Hypertension	3.33 (1.86–5.96)	0.0001
Fasting hyperinsulinaemia[a]	0.97 (0.46–2.06)	0.93
Dyslipidaemia[b]	0.79 (0.44–1.42)	0.43
Waist-to-hip ratio[c]	2.49 (1.09–5.70)	0.03
Non-diabetic subjects (n = 467)		
Impaired glucose tolerance	0.93 (0.43–2.00)	0.86
Hypertension	2.69 (1.25–5.75)	0.01
Fasting hyperinsulinaemia[a]	0.96 (0.34–2.68)	0.93
Dyslipidaemia[b]	0.77 (0.35–1.69)	0.51
Waist-to-hip ratio[c]	2.67 (1.04–5.75)	0.04
Diabetic subjects (n = 155)		
Hypertension	4.31 (1.60–11.56)	0.004
Fasting hyperinsulinaemia[a]	0.86 (0.26–2.86)	0.81
Dyslipidaemia[b]	0.72 (0.29–1.77)	0.74
Waist-to-hip ratio[c]	3.78 (0.41–34.74)	0.24

Age, sex, non-insulin-dependent diabetes mellitus, impaired glucose tolerance, hypertension, fasting hyperinsulinaemia, dyslipidaemia and waist-to-hip ratio were independent variables adjusted for each other; [a] the highest compared to the lowest tertile of fasting insulin levels, [b] defined as HDL-cholesterol in the lowest and/or triglycerides in the highest tertile, [c] the highest compared to the lowest tertile of waist-to-hip ratio per sex; OR = odds ratio; 95 % CI = 95 % confidence interval

Data analysis section; data not shown). We also investigated whether the association between MA and WHR was confounded by protein intake by performing analyses with daily protein intake (total, animal or vegetable; g/kg/day) in the regression model; there was no confounding (data not shown).

The above analyses suggested that hypertension and NIDDM were major determinants of MA, while other IRS-related variables were not. To investigate this issue further, we created two Z-scores (see Subjects and methods). The prevalence of MA increased

Fig. 2. Prevalence of microalbuminuria for different Z-scores. Z-score 1 is the sum of the Z-scores of systolic and diastolic blood pressure and fasting glucose levels, and Z-score 2 is the sum of the Z-scores of waist-to-hip ratio, fasting insulin, HDL-cholesterol and triglycerides levels

when the Z-score of glucose level and systolic and diastolic blood pressure increased, but not when the Z-score of the remaining IRS-related variables increased (Fig. 2). Sex- and age-adjusted regression analyses with these two Z-scores as independent variables showed a significant association with MA for the Z-score of blood pressure and fasting glucose (OR 1.89[1.32–2.70]), but not for the Z-score of the other IRS-related variables (OR = 1.39[0.98–2.00]). These results were similar for non-diabetic and diabetic subjects separately (data not shown).

We repeated the multiple regression analyses for the 174 subjects who had handed in two urine samples, for one sample only and for the mean of two samples. The results were similar, i. e. only hypertension and NIDDM were statistically significantly associated with MA (data not shown). We also investigated whether the definition of MA affected the results. However, the results of the multiple regression analyses were similar, whether MA was defined as an ACR over 2.5 mg/mmol for men and an ACR over 3.5 mg/mmol for women ([37]; prevalence, 7.7 % [48/622]), as an ACR 1.5 mg/mmol for both sexes ([4]; prevalence, 15.1 % [94/622]), or as ACR over 2.0 mg/mmol while excluding subjects with leukocyturia ($n = 136$; data not shown).

Discussion

This study shows that, in an ethnically homogeneous, Caucasian population aged 50–75 years, MA is strongly associated with hypertension, NIDDM and WHR, but not with other components of the IRS, i. e. insulin resistance, hyperinsulinaemia and dyslipidaemia. This suggests that MA is more likely to be a complication of NIDDM and (or) hypertension than a part of the IRS.

MA is thought to be a consequence of an increased leakage of albumin through the glomerular basement membrane as a result of increased intraglomerular capillary pressure, increased permeability of the glomerular capillary wall, or both [38]. Both hypertension and NIDDM can increase intraglomerular pressure [39]; hyperglycaemia, moreover, can induce loss of negative charges on the glomerular basement membrane and thus increase permeability to negatively charged proteins such as albumin [40]. Thus, there is a clear pathophysiological basis for the association of MA with NIDDM and hypertension, which strongly suggests that MA can arise as a complication of these phenomena. In contrast, there is no conclusive evidence that insulin resistance, hyperinsulinaemia or dyslipidaemia increase intraglomerular pressure and / or impair glomerular charge selectivity and thus lead directly to MA [41, 42]. Taken together, these findings argue against MA being an integral part of the IRS.

We did find that WHR, as a marker of central obesity, was associated with the presence of MA independently of NIDDM and hypertension. Recently, it has been reported that an increased urinary albumin excretion is associated with a higher body mass index [13]. One might argue that the association of central obesity with MA is consistent with the concept that MA is a part of the IRS. If this were the case, however, it is difficult to explain why MA turned out not to be associated with the other components of the IRS. In addition, several other mechanisms unrelated to the IRS may account for the association between central obesity and MA. Firstly, obese subjects may have a higher protein intake, which may increase the intraglomerular pressure [43]. In the present study, however, protein intake did not explain the association between WHR and MA. Secondly, recent data indicate that central adipose tissue may be a source of cytokines such as tumour necrosis factor-α [44], which can increase glomerular permeability [45]. Finally, through mechanisms that have not been elucidated, the overweight condition may be associated with renal haemodynamic changes, such as hyperperfusion and hyperfiltration, that tend to increase intraglomerular pressure [46].

Previous cross-sectional [6, 8, 11, 14] and prospective [9] studies have shown that IR, as determined with the euglycaemic hyperinsulinaemic clamp technique, was more severe in the presence of MA than in its absence. However, these studies were performed in highly selected subjects and cannot establish whether MA is intrinsically linked to IR and the IRS in the general population. Epidemiological studies of the associations of MA with IRS-related variables have not yielded consistent results [7, 10, 16, 18, 21–23]. In our study we found no association between MA and the IRS, even in Z-score analyses in which weak associations might reveal themselves by being

considered in combination. It is noteworthy that some studies that reported a positive association between MA and the IRS did not adjust for (central) obesity [6, 8, 14, 16], which would be desirable if (central) obesity was linked to MA through mechanisms independent of the IRS. In addition, the association between MA and the IRS may be different among different ethnic groups. It is remarkable that MA appears to be more closely related to hyperinsulinaemia and dyslipidaemia in non-diabetic populations with a low [10, 16] than in those with a high prevalence of hypertension [18, 21]. Thus, if a link between MA and the IRS does exist among non-diabetic subjects, it seems to be most prominent among populations with a low prevalence of hypertension.

Can methodological issues explain our results? Firstly, we collected only one urine sample from most subjects. As microalbuminuria is quite variable from day-to-day, this may have decreased the overall statistical power of the study. However, day-to-day variability is probably lessened somewhat by collecting overnight urine [47], as we did, and by expressing albumin excretion as an albumin-to-creatinine ratio [48]. In addition, analyses for the 176 subjects from whom two urine samples were collected yielded essentially similar results. Secondly, we chose an ACR over 2.0 mg/ mmol as the cut-off for MA. If the association between MA and the IRS would depend on a certain threshold for MA, we may have missed any such association by our choice of the threshold. However, analyses with a higher or a lower threshold gave similar results.

In conclusion, in an ethnically homogeneous, Caucasian population aged 50–75 years, the presence of microalbuminuria was associated with the presence of NIDDM and hypertension and with waist-to-hip circumference ratio, but not with other components of the IRS. We suggest that MA is not a useful marker of the IRS in Caucasian populations. This contrasts with data obtained in other ethnic groups [16]. Taken together, these findings suggest that the relationship between the IRS and MA may be modified by ethnicity or related factors, such as the prevalence of hypertension.

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