Factors affecting levels of urinary albumin excretion in the general population of Spain: the Di@bet.es study

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Abstract
The present study was undertaken to examine the prevalence of urinary ACR (albumin/creatinine ratio) > 30 mg/g and the associated clinical and environmental factors in a representative sample of the population of Spain. Di@bet.es study is a national, cross-sectional population-based survey conducted in 2009–2010. Clinical, metabolic, socio-demographic, anthropometric data and information about lifestyle habit were collected. Those subjects without KDM (known diabetes mellitus) were given an OGTT (oral glucose tolerance test). Albumin and creatinine were measured in a urinary sample and ACR was calculated. The population prevalence of ACR > 30 mg/g was 7.65 % (adjusted for sex and age). The prevalence of ACR > 30 mg/g increased with age (P < 0.001). Subjects with carbohydrate metabolism disorders had a greater prevalence of ACR > 30 mg/g but after being adjusted for age, sex and hypertension, was significant only in those subjects with UKDM (unknown diabetes mellitus) {OR (odd ratio), 2.07 [95 % CI (confidence interval), 1.38–3.09]; P < 0.001} and KDM [OR, 3.55 (95 % CI, 2.63–4.80); P < 0.001]. prevalence of ACR > 30 mg/g was associated with hypertension [OR, 1.48 (95 % CI, 1.12–1.95); P = 0.001], HOMA-IR (homoeostasis model assessment of insulin resistance) [OR, 1.47 (95 % CI, 1.13–1.92); P ≤ 0.01], metabolic syndrome [OR, 2.17 (95 % CI, 1.72–2.72); P < 0.001], smoking [OR, 1.40 (95 % CI, 1.06–1.83); P < 0.05], physical activity [OR, 0.68 (95 % CI, 0.54–0.88); P < 0.01] and consumption of fish [OR, 0.38 (95 % CI, 0.18–0.78); P ≤ 0.01]. This is the first study that reports the prevalence of ACR > 30 mg/g in the Spanish population. The association between clinical variables and other potentially modifiable environmental variables contribute jointly, and sometimes interactively, to the explanation of prevalence of ACR > 30 mg/g. Many of these risk factors are susceptible to intervention.

Key words: albumin/creatinine ratio, diabetes, epidemiology, microalbuminuria, prevalence, Spanish population
INTRODUCTION

Numerous studies have demonstrated the association between high levels of microalbuminuria and adverse health outcomes in adults. High microalbuminuria values in subjects with diabetes are associated with a higher risk for kidney disease and an increase in morbidity and mortality due to CVD (cardiovascular disease) [1]. The guidelines for the care of subjects with diabetes all recommend the systematic measurement of microalbuminuria, as an early intervention can reduce the risk associated with high microalbuminuria concentrations [2]. The clinical importance of microalbuminuria in the non-diabetic population is less well known. Microalbuminuria has been associated with different cardiovascular risk factors, such as hypertension, hypertriglyceridaemia and low HDL (high-density lipoprotein) levels, as well as increased cardiovascular morbidity, particularly in the presence of diabetes and hypertension [3]. Other studies suggest that high levels of microalbuminuria precede the onset of T2DM (Type 2 diabetes mellitus) and it is associated with abnormalities in the metabolic regulation of glucose and insulin [4].

The prevalence of microalbuminuria has been studied in different populations, and ranges from 6 to 11.6% [5–7]. However, the relation between microalbuminuria and environmental factors has been less well studied, though associations have been found with certain dietary components [8,9] and the socio-economic status [10].

The aim of the present study was to examine the prevalence of ACR (albumin/creatinine ratio) > 30 mg/g and the associated clinical and environmental factors in a representative sample of the population of Spain, as well as the association between ACR and certain clinical events and cardiovascular and metabolic risk factors.

MATERIALS AND METHODS

Population

The Di@bet.es study is a national cross-sectional population-based survey conducted in 2009–2010. The design and characteristics of the study have already been published [11]. A cluster sampling design was used to select participants with the target population being the entire Spanish population. Participants were randomly selected with a probability proportional to population size. Of the eligible adults, 55.8% attended for examination, of whom 9.9% were excluded by protocol (institutionalized, severe disease, pregnant or recent delivery), giving a final sample of 5072 individuals aged ≥ 18 years (41.6% men and 58.4% women).

The study was approved by the Ethics and Clinical Investigation Committee of Carlos Haya Hospital in addition to other regional ethics and clinical investigation committees all over Spain and written informed consent was obtained from all participants.

Variables and procedures

Participants were invited by mail and/or telephone to attend an examination visit at their health centre. Information was collected using an interviewer-administered structured questionnaire, followed by a physical examination by a nurse, who prior to the study had undergone a specific training course in order to standardize procedures. The field work was performed by seven teams each composed of a nurse and a dietician. After the interview, a fasting blood sampling, an OGTT (oral glucose tolerance test) and a urinary sampling were performed. All the field works was performed in the morning.

Socio-demographic data were collected (age and sex) as was information on smoking (current smoker or not current smoker) and physical activity during leisure time (never, at least once/week, 1–3 days/week and more than 3 days/week). Subjects were asked about changes in quantity or type of food in the last 6 months. Forty foods or food groups were identified and the frequency of their usual consumption was recorded [12].

Weight, height, waist and abdomen circumference were measured by standardized methods, and the BMI (body mass index) was calculated as weight/height². BP (blood pressure) was measured using a BP monitor (Hem-703C; Omron) after several minutes in a seated position; the mean of two measurements taken 1–2 min apart and was used for analysis.

Subjects with baseline capillary blood glucose levels lower than 7.8 mmol/l and those not currently receiving treatment for diabetes underwent a standard OGTT. Capillary blood glucose was measured at baseline and 2 h after the OGTT with a OneTouch® Ultra® glucose monitor (Lifescan), and a venous blood sample was taken from each subject (overnight fast and post load). Samples were immediately centrifuged and stored at −18°C (15 days maximum) until shipment to the centralized Ciberdem biobank where they were stored at −80°C for later analysis.

Serum glucose, TAG (triacylglycerol) and cholesterol were measured enzymatically, and HDL-cholesterol by direct method on an Architect C8000 Analyser (Abbott Laboratories). Serum insulin was measured by immunochemiluminescence in an Architect i8000 Analyser (Abbott Laboratories).

HOMA-IR (homoeostasis model assessment of insulin resistance) index was calculated as fasting serum insulin (m-units/ml) × fasting plasma glucose (mmol/l)/22.5 [13].

In 4463 people, a urinary sample was taken in the early morning hours and stored at −20°C for later analysis. The urinary

Abbreviations: ACR, albumin/creatinine ratio; BMI, body mass index; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; HDL, high-density lipoprotein; HOMA-IR, homoeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IGR, impaired glucose regulation; IGT, impaired glucose tolerance; KDM, known diabetes mellitus; OGTT, oral glucose tolerance test; OGTT-N, normal OGTT; OR, odds ratio; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus; TAG, triacylglycerol; UAE, urinary albumin excretion; UKDM, unknown diabetes mellitus.

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creatinine was measured using the modified Jaffe method (Randox Laboratories). The urinary albumin was measured by immunoturbidimetry (BioSystems). Creatinine and albumin were both measured using an A15 auto analyser from BioSystems (all those with serum creatinine \( \geq 176.8 \mu \text{mol/1} \) were excluded from the study).

The diagnosis and classification of diabetes was based on plasma glucose levels, using the 1999 World Health Organization criteria [14]. BMI \( \geq 30 \text{ kg/m}^2 \) was considered to represent obesity. Hypertension was defined as ongoing anti-hypertensive treatment or systolic BP \( \geq 140 \) and/or diastolic BP \( \geq 90 \text{ mmHg} \). Two BP readings were obtained and the average of the two measurements was used in the analyses. Insulin resistance was considered to be HOMA-IR values above the 75th percentile of the frequency distribution of the HOMA-IR values in the subjects without obesity and with OGTT-N (normal OGTT).

The metabolic syndrome was diagnosed following the NCEP ATP-III (National Cholesterol Education Program-Adult Treatment Panel III) criteria (2001). The UAE (urinary albumin excretion) was considered to be high when the albuminuria was \( > 30 \text{ mg/l} \) or the urinary ACR was \( > 30 \text{ mg/g} \) [15].

Statistical analysis
The hypothesis testing for continuous variables was done using ANOVA for two or more ways (or the Kruskal–Wallis test in the event of non-normality of distributions). Associations between the qualitative characteristics were tested by logistic regression analyses, controlling for age, sex and BMI to accommodate graded age, sex and BMI differences between the categories. In all cases the level of rejection of a null hypothesis was \( \alpha < 0.05 \).

RESULTS

General study characteristics and prevalence of high UAE
The mean age of the study population was 50 ± 17 years (range, 18–93); 42.9\% (\( n = 2174 \)) were men and 57.1\% (\( n = 2898 \)) women. Of this population, 9.5\% had KDM (known diabetes mellitus), 4.8\% had UKDM (unknown diabetes mellitus), 1.6\% had IFG (impaired fasting glucose) and IGT (impaired glucose tolerance), 6.1\% had IGT, 3.9\% had IFG and 74.1\% had OGTT-N. Of the subjects with KDM, 60.9\% were being treated with oral antidiabetic agents and 18.7\% with insulin; 10.9\% were taking both oral antidiabetic agents and insulin.

The population prevalence of UAE values \( > 30 \text{ mg/l} \) was 8.27\% (adjusted for sex and age) and that of ACR \( > 30 \text{ mg/g} \) was 7.65\% (adjusted for sex and age). The concordance between the two criteria, UAE \( > 30 \text{ mg/l} \) and ACR \( > 30 \text{ mg/g} \), was 97\% (\( \kappa = 0.75; P < 0.001 \)). Given this high concordance, the rest of the data analyses were just done with the ACR.

General study characteristics according to the ACR values
Table 1 summarizes the general characteristics of Di@bet.es study population and the association with ACR. Those subjects with an ACR \( > 30 \text{ mg/g} \) were older. After adjusting for age, the presence of T2DM, hypertension and obesity, only the systolic BP and plasma creatinine in men were significantly associated with the ACR levels.

Prevalence of high ACR according to sex and age
The prevalence of ACR \( > 30 \text{ mg/g} \) was 7.30\% in men and 7.99\% in women (adjusted for age). The prevalence of ACR \( > 30 \text{ mg/g} \) increased with age (\( P < 0.001 \)). In men, this increase was significant with effect from the age of 60 years and was independent of the greater prevalence of diabetes and hypertension with age; men aged 60–69 years: OR (odd ratio), 6.81 [95\% CI (confidence interval), 1.57–26.51 (\( P = 0.01 \))]; men aged 70–79 years: OR, 11.70 (95\% CI 2.69–50.86) (\( P = 0.001 \)); men aged > 80 years: OR, 14.09 (95\% CI 3.01–65.9) (\( P = 0.001 \)). The reference criteria for all three age groups was men < 30 years of age.

In women, though the prevalence of ACR \( > 30 \text{ mg/g} \) rose from the age of 70 years, the strength of association, measured by the OR, was not significant after adjusting the logistic model for the prevalence of diabetes and hypertension.

Association between ACR, diabetes and IGR (impaired glucose regulation)
Subjects with a carbohydrate metabolism disorder had a greater prevalence of ACR \( > 30 \text{ mg/g} \): OGTT-N, 5.8\%, IFG, 12.5\%, IGT, 9.9\%, IFG + IGT, 13.8\%, UKDM, 18.5\% and KDM, 28.4\%.

After adjusting the logistic regression model for age, sex and hypertension, the OR of having an ACR \( > 30 \text{ mg/g} \) compared with those subjects with an OGTT-N was significant for those with UKDM [OR, 2.07 (95\% CI, 1.38–3.09); \( P < 0.001 \)] and KDM [OR, 3.55 (95\% CI, 2.63–4.80); \( P < 0.001 \)]. No significant association was found, however, in the prevalence of ACR \( > 30 \text{ mg/g} \) for subjects with IGR (IFG, IGT or IFG + IGT) (results not shown).

Association between ACR and obesity
The prevalence of ACR \( > 30 \text{ mg/g} \) in obese subjects was 12.6\% compared with 7.3\% in the non-obese subjects (\( P < 0.001 \)). However, the strength of association lost significance after adjusting the logistic regression model for age, sex and the presence of diabetes [OR, 1.18 (95\% CI, 0.93–1.49)].

Association between ACR and hypertension
The prevalence of ACR \( > 30 \text{ mg/g} \) in subjects with hypertension was 14.1\% compared with 4.8\% in those without hypertension [OR, 1.48 (95\% CI, 1.12–1.95); \( P = 0.001 \)] adjusted for age, sex, obesity and diabetes.

Association between ACR and insulin resistance
Insulin resistance expressed as values higher than the 75th percentile in the frequency distribution of the HOMA-IR, was significantly associated with ACR \( > 30 \text{ mg/g} \), independently of age and sex [OR, 1.47 (95\% CI, 1.13–1.92); \( P < 0.01 \)], and after excluding subjects with KDM from the analysis. Nevertheless, the association lost significance after adjusting the model for...
Table 1  General characteristics of the Di@bet.es study population and the association with ACR levels

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ACR &lt;30 mg/g</th>
<th>ACR ≥30 mg/g</th>
<th>P value</th>
<th>P value (adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
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</tr>
<tr>
<td>Men</td>
<td>49 ± 16</td>
<td>63 ± 14</td>
<td>&lt;0.001</td>
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</tr>
<tr>
<td>Women</td>
<td>49 ± 16</td>
<td>58 ± 18</td>
<td>&lt;0.001</td>
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<tr>
<td>BMI (kg/m²)</td>
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<tr>
<td>Men</td>
<td>28.42 ± 4.28</td>
<td>30.47 ± 5.17</td>
<td>&lt;0.001</td>
<td>NS*</td>
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<tr>
<td>Women</td>
<td>27.44 ± 5.39</td>
<td>29.45 ± 6.67</td>
<td>&lt;0.001</td>
<td>NS*</td>
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<tr>
<td>Cholesterol (mmol/l)</td>
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</tr>
<tr>
<td>Men</td>
<td>5.05 ± 1.02</td>
<td>5.05 ± 1.05</td>
<td>NS</td>
<td>NS†</td>
</tr>
<tr>
<td>Women</td>
<td>5.10 ± 1.05</td>
<td>5.20 ± 1.00</td>
<td>NS</td>
<td>NS†</td>
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<tr>
<td>LDL-cholesterol (mmol/l)</td>
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<tr>
<td>Men</td>
<td>2.75 ± 0.80</td>
<td>2.70 ± 0.80</td>
<td>NS</td>
<td>NS†</td>
</tr>
<tr>
<td>Women</td>
<td>2.70 ± 0.80</td>
<td>2.70 ± 0.75</td>
<td>NS</td>
<td>NS†</td>
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<tr>
<td>TAG (mmol/l)</td>
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<tr>
<td>Men</td>
<td>1.53 ± 1.10</td>
<td>1.94 ± 1.74</td>
<td>&lt;0.001</td>
<td>0.05†</td>
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<tr>
<td>Women</td>
<td>1.16 ± 0.62</td>
<td>1.36 ± 0.64</td>
<td>&lt;0.001</td>
<td>&lt;0.05†</td>
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<tr>
<td>HDL-cholesterol (mmol/l)</td>
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<tr>
<td>Men</td>
<td>1.20 ± 0.30</td>
<td>1.15 ± 0.30</td>
<td>0.01</td>
<td>NS†</td>
</tr>
<tr>
<td>Women</td>
<td>1.45 ± 0.35</td>
<td>1.40 ± 0.35</td>
<td>NS</td>
<td>NS†</td>
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<tr>
<td>Uric acid (μmol/l)</td>
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</tr>
<tr>
<td>Men</td>
<td>359.87 ± 78.89</td>
<td>368.45 ± 95.71</td>
<td>NS</td>
<td>NS†</td>
</tr>
<tr>
<td>Women</td>
<td>236.60 ± 74.38</td>
<td>300.45 ± 110.11</td>
<td>&lt;0.001</td>
<td>NS†</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
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<tr>
<td>Men</td>
<td>136 ± 17</td>
<td>149 ± 21</td>
<td>&lt;0.001</td>
<td>&lt;0.05‡</td>
</tr>
<tr>
<td>Women</td>
<td>126 ± 19</td>
<td>140 ± 22</td>
<td>&lt;0.001</td>
<td>NS‡</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
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<tr>
<td>Men</td>
<td>79 ± 10</td>
<td>83 ± 11</td>
<td>&lt;0.001</td>
<td>NS†</td>
</tr>
<tr>
<td>Women</td>
<td>74 ± 11</td>
<td>79 ± 10</td>
<td>&lt;0.001</td>
<td>NS†</td>
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<tr>
<td>HOMA-IR</td>
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<tr>
<td>Men</td>
<td>2.19 ± 1.54</td>
<td>3.30 ± 3.18</td>
<td>&lt;0.001</td>
<td>NS$</td>
</tr>
<tr>
<td>Women</td>
<td>1.99 ± 2.55</td>
<td>2.14 ± 1.67</td>
<td>NS</td>
<td>NS$</td>
</tr>
<tr>
<td>Serum creatinine (μmol/l)</td>
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</tr>
<tr>
<td>Men</td>
<td>75.15 ± 12.40</td>
<td>81.40 ± 20.35</td>
<td>&lt;0.001</td>
<td>&lt;0.01‡</td>
</tr>
<tr>
<td>Women</td>
<td>61.00 ± 9.75</td>
<td>64.50 ± 14.15</td>
<td>&lt;0.001</td>
<td>NS†</td>
</tr>
<tr>
<td>Urinary creatinine (mmol/l)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>13.00 ± 5.95</td>
<td>9.80 ± 5.15</td>
<td>&lt;0.001</td>
<td>NS†</td>
</tr>
<tr>
<td>Women</td>
<td>10.10 ± 6.20</td>
<td>7.80 ± 5.90</td>
<td>&lt;0.001</td>
<td>NS†</td>
</tr>
</tbody>
</table>

*Adjusted for age, diabetes mellitus and hypertension.
†Adjusted for age, diabetes mellitus, hypertension and obesity.
‡Adjusted for age, diabetes mellitus and obesity.
$KDM excluded. Adjusted for age, IGR, hypertension and obesity.

hypertension and IGR (excluding those with KDM) [OR, 1.12 (95% CI, 0.84–1.15)].

Association between ACR and metabolic syndrome

Of those with the metabolic syndrome, 17.2% had an ACR >30 mg/g compared with 6.5% of those without the metabolic syndrome [OR, 2.17 (95% CI, 1.72–2.72); P < 0.001], after adjusting for age and sex. The model was not adjusted for obesity or diabetes as these variables were directly or indirectly contained in the definition of the metabolic syndrome.

Association between ACR and smoking

Of the whole sample, 26% were smokers. The OR of having an ACR >30 mg/g in those who smoked was 1.40 (95% CI, 1.06–1.83) (P ≤ 0.05). The model was adjusted for age, sex, obesity, hypertension and carbohydrate metabolism disorders (including diabetes). The OR of ACR >30 mg/g was dose
dependent, increasing significantly with effect from ten cigarettes/day \((P = 0.03)\) (Table 2).

In an ANOVA model, the log-ACR values were significantly higher with effect from ten cigarettes/day \((P < 0.001)\) (Figure 1, upper panel) (adjusted for age, sex, obesity, carbohydrate metabolism disorders and hypertension). This increase was particularly notable in the subjects with diabetes, with effect from 20 cigarettes/day the subjects with KDM had significantly higher log-ACR values (interaction carbohydrate metabolism disorders \(\times\) number of cigarettes, \(P < 0.05\)) (Figure 1, lower panel).

### Association between ACR and physical activity

Some type of physical exercise was performed by 38.1\% of the subjects on at least 1 day/week. The OR of having an ACR \(>30\) mg/g in those who undertook a sporting activity at least once/week was 0.68 (95\% CI, 0.54–0.88) \((P \leq 0.01)\), after adjusting for age, sex, obesity, hypertension and carbohydrate metabolism disorders. The log-ACR values were significantly higher in the subjects with diabetes who did not undertake any exercise (interaction carbohydrate metabolism disorders \(\times\) number of cigarettes, \(P \leq 0.05\)) (Figure 2). The negative association between exercise and the prevalence of ACR \(>30\) mg/g was visible with effect from just 1 day of exercise/week \((P \leq 0.001)\) (results not shown).

### Association between ACR and diet

Those subjects who consumed more fish were less likely to have an ACR \(>30\) mg/g. The strength of association between the consumption of fish and the prevalence of ACR \(>30\) mg/g was significant with effect from a consumption of fish on 10 days/month (Table 2 and Figure 3). A statistically significant interaction fish intake \(\times\) carbohydrate metabolism disorders was found \((P \leq 0.05)\). No other foodstuff of those studied was associated with the prevalence of ACR (results not shown).

### Overall model

Table 3 shows the two logistic regression models upon which the OR of having an ACR \(>30\) mg/g was calculated. Model A (reduced model) shows the OR for the clinical variables (sex, age, hypertension and diabetes). The second model (enlarged model) adds to Model A the environmental variables (fish consumption, physical activity and smoking). Model B significantly improved the explanation for the prevalence of ACR \(>30\) mg/g: likelihood ratio test, 2278.54 \(-\) 2255.61 = 22.93 (3 d.f.) \((\chi^2; P < 0.001)\).

### DISCUSSION

A high microalbuminuria level is considered a sensitive indicator of the glomerular basement membrane function and can be used as an early marker of progression to kidney disease, as well as cardiovascular death in both T1DM (Type 1 diabetes mellitus) and T2DM, and even in non-diabetic patients [15]. However, many of the risk factors associated with microalbuminuria are closely inter-related, and it is often difficult to establish the independence of the association. The present study was undertaken in a representative sample of the Spanish population, with careful identification of the clinical phenotypes usually related with...
The prevalence of high UAE (e.g. IGR and diabetes by systematic performance of an OGTT) and close consideration of other environmental variables. The results show that in the general population the prevalence of ACR > 30 mg/g is conditioned not only by well-known clinical factors but also by certain interacting environmental factors.

Numerous studies have examined the prevalence of microalbuminuria in different populations. The Third National Health and Nutrition Examination Survey in the U.S.A. reported a prevalence of 6.1% for men and 9.7% for women [5]. Other prevalence rates include 11.4% in the Seychelles [6] and 11.5% in Taiwan [16]. A recent study in the general population in China found the prevalence of microalbuminuria to be 8.8% [7]. The prevalence of ACR > 30 mg/g in our study was 8.79% (7.65% after adjusting for sex and age).

The prevalence of ACR > 30 mg/g was higher in men than in women, as has been found in some earlier studies [5,16,17], but not others [7], some of which even found the prevalence to be lower in men than in women [6]. It is for this reason that a few authors have proposed a sex-related cut-off value to define high microalbuminuria level, though to date no agreement has been reached [18]. These differences have been attributed, among other reasons, to differences in the urinary concentration of creatinine between men and women.

In most studies, the prevalence of high microalbuminuria rises with age [5], as it did in ours. A linear relation between age and ACR values has been reported in men but not women in Denmark [19]. The reduction in urinary creatinine with age may contribute to this increase. However, in our present study, the reduction in creatinine is linear with effect from the age of 18 years, whereas the increase in the prevalence of high microalbuminuria levels starts with effect from the age of 50–60 years. Thus age by itself (at least in women) does not appear to contribute independently to the increase in ACR, as this increase was due in great part to the increased prevalence of diabetes and hypertension with age, as after suppressing from the analysis those subjects with hypertension and diabetes, the significant association between age and ACR > 30 mg/g disappeared. The increased prevalence of microalbuminuria in older subjects may also be due to the presence of unconsidered concomitant diseases that could affect glomerular filtration [20].

Most studies, including ours, have found an association between the prevalence of microalbuminuria, hypertension [5,7,21] and diabetes [5,7,22]. Prevalence rates of microalbuminuria of 39% [23], 28.8% [5] and 25.3% [24] have been reported for large series of subjects with diabetes. The inclusion of subjects with different stages of diabetes may account for the differences between studies. In our study the prevalence of ACR > 30 mg/g in subjects with KDM was 28.4% and in those with UKDM it was 18.5%. Few studies have examined the prevalence of microalbuminuria in subjects with prediabetes. In a study undertaken in Australia, Tapp et al. [24] found prevalence rates of microalbuminuria in subjects with OGTT-N, IGR, IGT, UKDM and KDM of 4.7%, 8.8%, 7.6%, 10.6% and 22.2%,

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**Table 3: Logistic regression models**

<table>
<thead>
<tr>
<th>Model</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model A (reduced model)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.028 (1.019–1.036)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td>1.060 (0.847–1.326)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.540 (1.170–2.029)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>T2DM</td>
<td>2.771 (2.150–3.571)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model B (enlarged model)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.030 (1.021–1.039)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td>1.075 (0.855–1.350)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.555 (1.180–2.049)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>T2DM</td>
<td>2.711 (2.101–3.500)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.310 (0.990–1.735)</td>
<td>NS</td>
</tr>
<tr>
<td>Physical activity</td>
<td>0.690 (0.540–0.882)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fish consumption</td>
<td>0.521 (0.272–0.998)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
respectively, although the association with the risk for kidney disease as measured by the microalbuminuria disappeared in those subjects with IFG after adjusting for other related variables. In our study, only those subjects with UKDM and KDM had a greater likelihood of having an elevated ACR, independently of age and hypertension.

Suggestions have been made that the appearance of microalbuminuria precedes the risk of T2DM [4]. T2DM is a disease that develops over a long time and which is preceded by a long preclinical period in the form of insulin resistance or IGR. Taken together, the results of our study show that an ACR > 30 mg/g only appears when the diabetes is evident, either analytically (UKDM) or clinically (KDM), suggesting that the onset of microalbuminuria is simultaneous with the onset of diabetes.

Studies have also found an independent association between microalbuminuria and obesity or insulin resistance [7]. Several studies suggest that insulin resistance precedes, and probably contributes to, the increase in microalbuminuria in subjects with T1DM [25] and T2DM [26], as well as in non-diabetic subjects [27]. Other studies, however, have found no association between microalbuminuria and insulin resistance in healthy subjects [28]. Contradictory results have also been reported about the possible association in the general population between insulin resistance and an increased UAE, with some only finding this association in men [29].

In our present study neither obesity nor insulin resistance were associated with an ACR > 30 mg/g independently of the presence of hypertension or IGR, though a solid association was seen with the metabolic syndrome. This association between ACR and the metabolic syndrome has also been found in other studies [30].

Different studies have shown the adverse effect of smoking on levels of microalbuminuria in subjects without diabetes [31] and those with T1DM [32] and T2DM [33]. Patients with hypertension who smoke may have an increased risk for microalbuminuria, even before the onset of other haemodynamic disorders [34]. In our study, the subjects who smoked had higher levels of ACR. Moreover, this effect was dose-dependent, becoming significant with effect from 20 cigarettes/day, a similar number to that found elsewhere [33]. This occurred in subjects with OGTT-N as well as in subjects with KDM, in whom the increase occurred at the expense of an interaction between the presence of hypertension, diabetes and smoking. This is of particular interest in the clinical setting for the design of intensive education programmes.

The effects of exercise on kidney function are contradictory. In our present study physical exercise was associated with a lower risk for a raised ACR. Some studies have shown a close relation between physical exercise and the GFR (glomerular filtration rate), but no association with microalbuminuria [35]. In patients with diabetes acute exercise seems to increase the excretion of microalbuminuria in some studies [36], though not all [37]. In subjects with T2DM, aerobic training reduces microalbuminuria [38]. The beneficial effect of physical exercise in our study was independent of the presence of diabetes, IGR, hypertension or other risk factors for microalbuminuria.

Of particular interest is the relation between diet and the risk for microalbuminuria. A high intake of foods poor in fat and rich in cereals and fruit is associated with a lower OR of microalbuminuria [8]. Studies related to the consumption of fish and the risks of microalbuminuria are few. One study found no relation between the intake of n-3 fatty acids and levels of microalbuminuria [39], whereas another study found an inverse association between fish consumption and the risk for microalbuminuria in subjects with diabetes (but not in healthy subjects) [9]. In our study subjects who consumed more fish had a lower frequency of ACR > 30 mg/g.

The measurement of microalbuminuria has proved to be useful as an indicator of the integrity of the glomerular basement membrane. There are multiple mechanisms by which the various clinical or environmental situations are associated with the OR of a high ACR, though many are related to the worsening glomerular permeability in the case of diabetes or hypertension, or the effect on the physiology of the membrane and endothelial dysfunction in the case of smoking, exercise or dietary fatty acids [40,41].

The present study has a few limitations, such as its cross-sectional design, which prevents any relation of causality to be established. ACR was measured in a single urinary sample, so false positives cannot be ruled out. However, exclusion criteria were very strict and subjects with acute illness at the moment of the evaluation were excluded. On the other hand, other population-based studies have found no significant differences even though microalbuminuria was measured once [42]. Finally, recent studies have shown that cut-off levels lower than 30 mg/g are also a cardiovascular risk factor in hypertensive subjects, so a change in the microalbuminuria cut-off levels may vary the prevalence [42].

Many of the risk factors for having ACR > 30 mg/g are interrelated, which would explain some of the discrepancies found in the literature. Di@bet.es study was undertaken in a representative sample of the Spanish population in whom careful phenotyping was done of the risk factors associated with the onset of high ACR values, simultaneously with the evaluation of different environmental factors, in an attempt to provide a fuller explanation of the causes of elevated ACR in the general population. The results show that together with the association of clinical variables such as diabetes, hypertension, or the metabolic syndrome, other potentially modifiable environmental variables also contribute jointly, and sometimes interactively, with the clinical variables to the explanation of the appearance of elevated albuminuria. Many of these risk factors are susceptible to intervention. The modification of risk factors via lifestyle interventions, together with other measures to control the clinical variables, may impact on the prevention of complications, save money and improve the quality of life of these patients.

**CLINICAL PERSPECTIVES**

- A high microalbuminuria value is an early marker of diabetes risk and its complications as well as of CVD. The Di@bet.es study was undertaken in a representative sample of the Spanish population to determine ACR epidemiology and its conditioning factors in the Spanish population.
- The population prevalence of ACR >30 mg/g was 7.65%, increased with age and was positively associated with
hypertension, HOMA-IR, the metabolic syndrome and smoking, whereas it was negatively associated with physical activity and consumption of fish.

• By knowing the conditioning factors of ACR >30 mg/g in the Spanish population, strategies can be designed to prevent the appearance of ACR >30 mg/g as a metabolic and cardiovascular risk factor.

AUTHOR CONTRIBUTION
All the authors contributed to the interpretation of data, discussion of results and critical review, and gave final approval of the version to be published.

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