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ORIGINAL ARTICLE

Independent correlates of urinary albumin excretion within the normoalbuminuric range in patients with type 2 diabetes: The Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study

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Abstract

Aims Within the normoalbuminuric range, low albuminuria (LA, 10–29 mg/24 h) is associated with higher adverse cardiovascular and renal outcomes than normal albuminuria (NA, <10 mg/24 h). This cross-sectional analysis of the cohort from the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study was aimed at assessing the independent correlates of LA versus NA in patients with type 2 diabetes.

Methods This analysis involved 11,538 normoalbuminuric patients (73.2 % of the entire RIACE cohort): 6023 (52.2 %) with NA and 5515 (47.8 %) with LA. Binary logistic regression analysis with backward conditional variable selection was applied to assess the independent correlates of LA versus NA.

Results Compared with NA subjects, LA patients were more frequently males, older and with family history of hypertension, had longer diabetes duration, lower HDL cholesterol, and higher haemoglobin (Hb) A_{1c}, triglycerides, and blood pressure (BP), use of anti-hyperglycaemic and anti-hypertensive drugs, and prevalence of metabolic syndrome, retinopathy, chronic kidney disease, any cardiovascular disease, myocardial infarction, and coronary and peripheral events. Men with LA were also more frequently current or former smokers and had higher body mass index, waist circumference, and non-HDL cholesterol. Independent correlates of LA were age (OR 1.018), family history of hypertension (OR 1.321), smoking status (former, OR 1.158; current, OR 1.237), HbA_{1c} (OR 1.062), waist circumference (OR 1.050), triglycerides

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(OR 1.001), and diastolic BP (OR 1.014), together with use of anti-hyperglycaemic and anti-hypertensive agents.
Conclusions Several risk factors are associated with increased albuminuria within the normoalbuminuric range. As most of these factors are potentially modifiable, treating them aggressively might reduce the excess risk associated with LA.
Trial registration NCT00715481; www.ClinicalTrials.gov.

Keywords Albumin excretion rate · Type 2 diabetes · Chronic kidney disease · eGFR · Diabetic retinopathy

Abbreviations

AER	Albumin excretion rate
ACR	Albumin-to-creatinine ratio
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
DM	Diabetes mellitus
T2DM	Type 2 DM
RIACE	Renal insufficiency and cardiovascular events
NA	Normal albuminuria
LA	Low albuminuria
T1DM	Type 1 DM
ROADMAP	Randomised Olmesartan and Diabetes Microalbuminuria Prevention
BP	Blood pressure
BMI	Body mass index
MS	Metabolic syndrome
HbA_{1c}	Haemoglobin A_{1c}
CKD	Chronic kidney disease
DR	Diabetic retinopathy
OHA	Oral hypoglycaemic agents
RAS	Renin–angiotensin system
DHP	Dihydropyridine
PP	Pulse pressure
OR	Odds ratio
CI	Confidence interval

Introduction

Increased urinary albumin excretion rate (AER) is associated with an increased risk of adverse cardiovascular and renal outcomes, even within the normoalbuminuric range. In a collaborative meta-analysis of general population cohorts, a urinary albumin-to-creatinine ratio (ACR) of 10–29 mg/g was associated with a 48 and 63 % excess risk of death for all-cause and cardiovascular disease (CVD), respectively, as compared to an ACR of <10 mg/g, at an estimated glomerular filtration rate (eGFR) of 90–104 mL/min/1.73 m^2 [1]. Two other meta-analyses showed that an ACR of 10–29 mg/g is a risk factor for all-cause and CVD mortality also in high-risk and low-risk populations, such as individuals with and without hypertension [2] and diabetes mellitus (DM) [3]. Finally, in all these settings [1–3], an ACR of 10–29 mg/g was an independent predictor of mortality for any category of eGFR, as compared to an ACR of <10 mg/g.

Risk of CVD events also increases linearly with increases in albuminuria within the normoalbuminuric range, with no threshold, as consistently demonstrated in post hoc analyses of randomized trials in high-risk individuals [4, 5], as well as in community-based cohort studies [6, 7]. Finally, in subjects with type 2 DM (T2DM) from the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study, the excess CVD risk became significant starting from AER values ≥10.5 mg/24 h [8].

Several longitudinal studies have evaluated the determinants of AER progression in patients with type 1 DM (T1DM) [9–12] and T2DM [13, 14]. However, only a cross-sectional analysis of a cohort of 4449 T2DM patients from an intervention trial, the Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study, has investigated the correlates of ACR across the normoalbuminuric range [15].

In 2009, a new classification of albuminuria has been proposed [16]. In this classification, in addition to high albuminuria (i.e. AER 30–299 mg/24 h or ACR 30–299 mg/g, currently termed microalbuminuria) and very high albuminuria (i.e. AER ≥ 300 mg/24 h or ACR ≥ 300 mg/g, currently termed macroalbuminuria), a threshold has been set at AER 10 mg/24 h or ACR 10 mg/g to distinguish normal albuminuria (NA, i.e. AER < 10 mg/24 h or ACR < 10 mg/g) from low albuminuria (LA, i.e. AER 10–29 mg/24 h or ACR 10–39 mg/g) within the normoalbuminuric range, in order to account for the increased CVD and renal risk associated with LA versus NA.

This cross-sectional analysis of the even larger RIACE cohort was aimed at assessing the independent correlates of LA versus NA in T2DM patients in real-life conditions.

Subjects and methods

Patients

In this cross-sectional analysis, we used the data collected at the baseline visit for the RIACE Italian Multicentre Study using standardized protocols across study centres. The RIACE Study is an observational, prospective cohort

study on the impact of eGFR on morbidity and mortality from CVD in subjects with T2DM [17]. The study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. The protocol was approved by the locally appointed ethics committees, and participants gave informed consent.

The RIACE cohort consisted of 15,773 Caucasian patients with T2DM (defined by the American Diabetes Association criteria), attending consecutively 19 hospital-based Diabetes Clinics of the National Health Service throughout Italy (see online appendix) in years 2007–2008. Exclusion criteria were dialysis or renal transplantation.

Measurements

All patients underwent a structured interview in order to collect the following information: age; smoking status; known DM onset and duration; and current glucose-, blood pressure (BP)-, and lipid-lowering therapy. Body mass index (BMI) was calculated from weight and height, and BP was measured with a mercury sphygmomanometer with the patients seated with the arm at the heart level. Hypertension was defined by systolic BP $\geq$ 140 mmHg and/or diastolic BP $\geq$ 90 and/or anti-hypertensive treatment. Waist circumference was measured in 4618 subjects and estimated in the remaining 11,155 individuals from log-transformed BMI value, as previously described [18]. The absolute waist circumference was used as measure of central obesity, and the metabolic syndrome (MS) was defined according to the National Cholesterol Education Program Adult Treatment Panel III criteria [19].

Haemoglobin (Hb) A_{1c} was measured by high-performance liquid chromatography; triglycerides, total, and HDL cholesterol were determined in fasting blood samples by colorimetric enzymatic methods; and LDL cholesterol was calculated by the Friedwald formula. The same methods were used during the study period by all centres. Dyslipidemia was defined by LDL cholesterol $\geq$2.59 mmol/L and/or treatment with lipid-lowering agents.

The presence of chronic kidney disease (CKD) was assessed by measuring albuminuria and serum creatinine. As previously detailed [20, 21], AER was obtained from 24-h urine collections or calculated from ACR in early-morning, first-voided urine samples. Albuminuria was measured in one to three fresh urine samples for each patient by immunonephelometry or immunoturbidimetry, and in case of multiple measurements, the geometric mean was used for analysis. In subjects with multiple measurements (4062 with at least two and 2310 with three values), concordance rate between the first value and the geometric mean was >90 % for all classes of albuminuria [21]. Serum (and urine) creatinine was measured by the modified Jaffe method. One to three measurements were taken for each patient, and eGFR was calculated by the Epidemiology Collaboration (CKD-EPI) equation [22] using the mean serum creatinine value in case of multiple measures [20, 21]. In this report, only subjects with normoalbuminuria were included. Normoalbuminuric patients with an eGFR $<$ 60 mL/min/1.73 m^2 were classified as having non-albuminuric CKD [20], an increasingly frequent phenotype of renal impairment [23].

In each centre, the presence of diabetic retinopathy (DR) was assessed by an expert ophthalmologist with dilated fundoscopy. Patients were classified into absent DR; mild, moderate, or severe non-proliferative DR; proliferative DR; or maculopathy. For further analysis, patients with mild or moderate non-proliferative DR were classified as having non-advanced DR, whereas those with severe non-proliferative DR, proliferative DR, maculopathy, or blindness were grouped into the advanced, sight-threatening DR category [24].

Prevalent CVD was assessed from medical history by recording previous documented major acute CVD events, including myocardial infarction, stroke, foot ulcer/gangrene/amputation, coronary, carotid, and lower limb revascularization. CVD events were adjudicated based on hospital discharge records by an ad hoc committee in each centre [8].

Statistical analysis

Data are expressed as mean $\pm$ SD, for continuous variables, and number of cases and percentage for categorical variables. Continuous variables were compared by the Student's *t* test, for normally distributed variables, or the Wilcoxon sum of ranks (Mann–Whitney) test, in case of variables with a skewed distribution. Pearson *Chi-square* was applied to categorical variables.

Binary logistic regression analysis with backward conditional variable selection (probability for removal >0.10) was applied to assess the independent association of several continuous and categorical variables with LA versus NA. Independent continuous covariates were age, T2DM duration, HbA_{1c}, BMI, waist circumference, total cholesterol, HDL cholesterol, triglycerides, and systolic and diastolic BP, whereas independent categorical variables were gender, smoking habits, DR, family histories of T2DM, hypertension and CVD, and use of anti-hyperglycaemic drugs [oral hypoglycaemic agents (OHA) and/or insulin], blockers of the renin-angiotensin system (RAS), and dihydropyridine (DHP) Ca-channel blockers. The logistic regression model was repeated after excluding subjects with CKD or after substitution of central obesity for waist circumference or of pulse pressure (PP) for systolic BP. Results were expressed as odds ratios (ORs) with

their 95 % confidence intervals (CIs). A p value (two sided) of <0.05 was considered statistically significant.

Statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Of the 15,773 RIACE participants, 11,538 (73.1 %) had normoalbuminuria, while the remaining 4235 had microalbuminuria ($n = 3497$, 22.2 %) or macroalbuminuria ($n = 738$, 4.7 %) [20]. Of the 11,538 patients with normoalbuminuria, 6023 (52.2 %) had NA and 5515 (47.8 %) had LA (Fig. 1). Among the 6102 (52.9 %) men, 2993 (49.0 %) had NA and 3109 (51.0) had LA, whereas among the 5436 (47.1 %) women, 3030 (55.7 %) had NA and 2406 (44.3 %) had LA.

Compared with patients with NA, those with LA were more frequently males and older, had longer T2DM duration, higher HbA_{1c}, triglycerides, systolic and diastolic BP, and lower HDL cholesterol and eGFR. LA subjects had also higher prevalence of family history of hypertension, hypertension, and use of anti-hyperglycaemic (OHAs and/or insulin) and anti-hypertensive (including RAS blockers and DHP Ca-channel blockers) drugs (Table 1). Only in men, prevalence of obesity and central obesity, BMI, waist circumference, non-HDL cholesterol, and percentage of current and former smokers were higher in LA versus NA patients (Supplemental Table 1).

Patients with LA had higher prevalence of CKD and non-advanced and advanced DR (Table 2). Though eGFR correlated significantly with AER ($p < 0.0001$), prevalence of LA increased only from eGFR category 3b (i.e. <45 mL/min/1.73 m^2). Moreover, patients with LA had a higher prevalence of any major acute CVD event, myocardial infarction, ulcer/gangrene/amputation, and any coronary and peripheral vascular event. After stratification by gender, LA was associated with any coronary event in males, and with any peripheral event and ulcer/gangrene/amputation in females. No differences were observed in the prevalence of any cerebrovascular event and stroke in the whole population as well as in females, whereas stroke was slightly more frequent among males with LA (Table 2 and Supplemental Table 2).

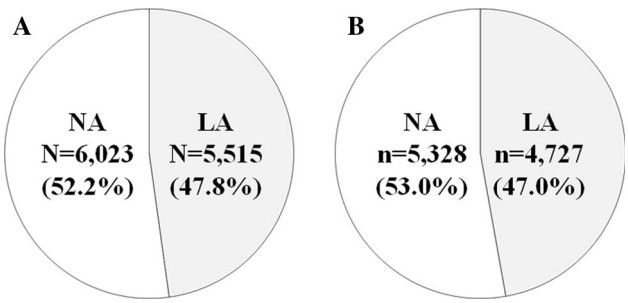

Fig. 1 Distribution of NA (AER < 10 mg/24 h) and LA (AER 10 to <30 mg/24 h) among the 11,538 T2DM subjects with normoalbuminuria (**a**) and the 10,055 T2DM subjects with normoalbuminuria and an eGFR > 60 mL/min/1.73 m^2 (no CKD) (**b**). *NA* normal albuminuria, *LA* low albuminuria, *AER* albumin excretion rate, *eGFR* estimated glomerular filtration rate, *T2DM* type 2 diabetes mellitus, *CKD* chronic kidney disease

Logistic regression analysis with backward variables selection showed an independent correlation of LA with male gender, age, family history of hypertension, former and current smoking status, HbA_{1c}, triglycerides, diastolic BP, use of DHP Ca-channel blockers and OHAs and/or insulin, and non-advanced DR. Furthermore, marginally significant correlations were observed for waist circumference, use of RAS blockers, and, inversely, family history of CVD (Table 3). When excluding the 1483 normoalbuminuric subjects with CKD, the allocation to NA ($n = 5328$, 53.0 %) and LA ($n = 4727$, 47.0 %) did not change (Fig. 1), as similar were the differences in clinical features and prevalence of complications between the two groups (data not shown). In the regression analysis, total cholesterol (OR 1.001) entered as a new independent correlate of LA, triglycerides became only marginally significant, and family history of CVD was no longer a significant covariate (Table 3). When substituted for systolic BP, PP did not enter in the model, except when only females were considered (data not shown).

When analysed separately by gender, some correlates of LA, such as age, family history of hypertension, diastolic BP, and use of OHAs and/or insulin, were common to both males and females. In contrast, waist circumference (and central obesity), smoking status, HbA_{1c}, total cholesterol, use of RAS and DHP Ca-channel blockers, and, inversely, family history of CVD correlated independently with LA only in men, whereas triglycerides, non-advanced and advanced DR, and, in the whole cohort only, systolic BP were associated with LA only in women (Table 4).

Discussion

This analysis of the RIACE cohort provides further insights into the correlates of higher AER levels within the normoalbuminuric range, which are associated with an increased risk of adverse CVD and renal outcomes, as compared to lower values [1–8].

Consistent with this increased risk, LA subjects with T2DM from the RIACE cohort had a higher prevalence of any acute major CVD as compared to NA patients. Moreover, the excess risk of any CVD event associated with LA was slightly higher, though not significantly ($p = 0.57$), in males (OR 1.273, 95 % CI 1.131–1.433,

Table 1 Clinical features of normoalbuminuric subjects, as a whole and divided according to AER levels in patients with NA and LA

	Total	NA	LA	*P*
N (%)	11,538 (100)	6023 (52.2)	5515 (47.8)	
Males, *n* (%)	6102 (52.9)	2993 (49.7)	3109 (56.5)	<0.0001
Age, years	65.5 ± 10.3	64.8 ± 10.3	66.2 ± 10.2	<0.0001
Family history of diabetes, *n* (%)	5492 (47.6)	2872 (47.7)	2620 (47.5)	0.841
Family history of hypertension, *n* (%)	2523 (21.9)	1220 (20.3)	1303 (23.6)	<0.0001
Family history of CVD, *n* (%)	1346 (11.7)	730 (12.1)	616 (11.2)	0.112
Smoking habits, *n* (%)				
No smokers	6799 (58.9)	3709 (61.6)	3090 (56.0)	<0.0001
Former smokers	3076 (26.7)	1492 (24.8)	1584 (28.7)	<0.0001
Current smokers	1663 (14.4)	822 (13.6)	841 (15.2)	0.014
Known duration of diabetes, years	12.5 ± 10.0	12.1 ± 9.8	12.8 ± 10.1	<0.0001
HbA_{1c}, % (nmol/mol)	7.43 ± 1.42 (57.7 ± 15.5)	7.35 ± 1.35 (56.8 ± 14.8)	7.51 ± 1.49 (58.6 ± 16.3)	<0.0001
Glucose-lowering treatment, *n* (%)				
Lifestyle	1750 (15.2)	1048 (17.4)	702 (12.7)	<0.0001
OHA	7285 (63.1)	3756 (62.4)	3529 (64.0)	0.070
Insulin + OHA	983 (8.5)	490 (8.1)	493 (8.9)	0.122
Insulin	1520 (13.2)	729 (12.1)	791 (14.3)	<0.001
BMI, kg/m^2	28.8 ± 5.1	28.7 ± 5.1	28.9 ± 5.1	0.043
Overweight, *n* (%)	4867 (42.2)	2547 (42.3)	2320 (42.1)	0.806
Obese, *n* (%)	3979 (34.5)	2027 (33.7)	1952 (35.4)	0.049
Waist circumference, cm	102.0 ± 10.3	101.7 ± 10.2	102.3 ± 10.3	0.003
Central obesity, *n* (%)	7729 (67.0)	4050 (67.2)	3679 (66.7)	0.543
Triglycerides, mmol/L	1.50 ± 0.90	1.48 ± 0.90	1.53 ± 0.90	<0.001
Total cholesterol, mmol/L	4.79 ± 0.97	4.79 ± 0.96	4.80 ± 0.98	0.636
HDL cholesterol, mmol/L	1.31 ± 0.35	1.32 ± 0.35	1.30 ± 0.35	<0.001
LDL cholesterol, mmol/L	2.80 ± 0.84	2.80 ± 0.83	2.81 ± 0.85	0.613
Non-HDL cholesterol, mmol/L	3.48 ± 0.93	3.47 ± 0.92	3.50 ± 0.94	0.613
Dyslipidemia, *n* (%)	9498 (82.3)	4932 (81.9)	4566 (82.8)	0.203
Lipid-lowering treatment, *n* (%)	5219 (45.2)	2719 (45.1)	2500 (45.3)	0.841
Systolic BP, mmHg	137.1 ± 17.5	136.2 ± 17.5	138.2 ± 17.6	<0.0001
Diastolic BP, mmHg	78.6 ± 9.2	78.1 ± 9.3	79.2 ± 9.1	<0.0001
Hypertension, *n* (%)	9338 (80.9)	4764 (79.1)	4574 (82.9)	<0.0001
Anti-hypertensive treatment, *n* (%)	7666 (66.4)	3878 (64.4)	3788 (68.7)	<0.0001
RAS blockers, *n* (%)	6175 (53.5)	3090 (51.3)	3085 (55.9)	<0.0001
DHP Ca-channel blockers, *n* (%)	1730 (15.0)	813 (13.5)	917 (16.6)	<0.0001
MS, *n* (%)	8275 (71.7)	4261 (70.7)	4014 (72.8)	0.015
Serum creatinine, μmol/L	80.4 ± 24.8	78.7 ± 20.3	81.3 ± 28.3	<0.0001
eGFR, mL/min/1.73 m^2	82.9 ± 19.1	83.5 ± 18.4	82.3 ± 19.8	0.001

AER albumin excretion rate, *NA* normal albuminuria, *LA* low albuminuria, *CVD* cardiovascular disease, *HbA_{1c}* haemoglobin A_{1c}, *OHA* oral hypoglycaemic agent, *BP* blood pressure, *RAS* renin–angiotensin system, *DHP* dihydropyridine, *MS* metabolic syndrome, *eGFR* estimated glomerular filtration rate

$p < 0.0001$) than in females (OR 1.206, 95 % CI 1.040–1.398, $p = 0.013$), consistent with the absence of interaction with sex observed for CVD mortality in the same meta-analysis [3]. We also evaluated CVD events by vascular bed and found that LA was associated with any coronary event and with myocardial infarction as well as with any peripheral vascular event and with ulcer/gangrene/amputation, but not with any cerebrovascular event or stroke. The association with coronary events is consistent with previous reports from the Losartan Intervention For Endpoint reduction study [7] and the Third Copenhagen City Heart Study [25].

LA patients from the RIACE cohort also showed an increased prevalence of CKD and DR, as compared to

Table 2 Prevalence of complications among subjects, as a whole and divided according to AER levels in patients with NA and LA

	Total	NA	LA	*P*
N (%)	11,538 (100)	6023 (52.2)	5515 (47.8)	
CKD, *n* (%)				
No CKD	10,055 (87.1)	5328 (88.5)	4727 (85.7)	<0.0001
CKD	1483 (12.9)	695 (11.5)	758 (14.3)	<0.0001
DR, *n* (%)				
No	9462 (82.0)	5030 (83.6)	4432 (80.3)	<0.0001
Non-advanced	1264 (11.0)	599 (9.9)	665 (12.1)	0.0003
Advanced	812 (7.0)	394 (6.5)	418 (7.6)	0.029
Any major acute CVD event, *n* (%)	2285 (19.8)	1077 (17.9)	1208 (21.9)	<0.0001
Coronary events, *n* (%)				
Any event	1578 (13.7)	753 (12.5)	825 (15.0)	<0.0001
Myocardial infarction	1145 (9.9)	560 (9.3)	585 (10.6)	0.019
Cerebrovascular events, *n* (%)				
Any event	765 (6.6)	380 (6.3)	385 (7.0)	0.147
Stroke	301 (2.6)	141 (2.3)	160 (2.9)	0.067
Peripheral vascular events, *n* (%)				
Any event	475 (4.1)	216 (3.6)	259 (4.7)	0.003
Ulcer/gangrene/amputation	255 (2.2)	104 (1.7)	151 (2.7)	<0.0001

AER albumin excretion rate, *NA* normal albuminuria, *LA* low albuminuria, *CKD* chronic kidney disease, *DR* diabetic retinopathy, *CVD* cardiovascular disease

those with NA. In this regard, an association of ACR with progressive CKD and mortality was recently reported in a nationally representative cohort of US veterans; this association appeared to increase linearly at ACR levels $\geq$10 mg/g, mainly in the presence of DM [26]. Moreover, recent small-sized cross-sectional studies showed that the higher tertile of AER within the normoalbuminuric range was independently associated with the presence of DR in patients with T2DM [27, 28] and pre-clinical diabetic glomerulopathy lesions correlated with severity of DR in normoalbuminuric subjects with T1DM [29].

Regarding the primary aim of our analysis, i.e. the assessment of the independent correlates of LA, logistic regression analyses showed that multiple factors are associated with higher AER values within the normoalbuminuric range.

Among indices of glycemic control, HbA_{1c} and use of anti-hyperglycaemic drugs were independently associated with LA, and when analysed by gender, the correlation with HbA_{1c} was significant only in men, whereas that with glucose-lowering treatments, it was stronger in females than in males. However, at variance with the ROADMAP study [15], we did not find an association of LA with DM duration, possibly because it was masked by the strong correlation with age.

In our analysis, we also found an association with diastolic BP, but not with systolic BP or PP, again at variance with the ROADMAP study [15]. In this latter study, it was also reported that the sub-cohort with higher night-time than day-time systolic BP at ambulatory BP monitoring had higher ACR levels, as compared to subjects with lower night-time than day-time systolic BP [15], a finding consistent with studies in both T1DM [30] and T2DM [31] showing that higher night-time systolic BP precedes the development of microalbuminuria. The ROADMAP study also documented a relationship of albuminuria with PP, an index of vascular stiffness [15], in keeping with the findings that, in T2DM, increased carotid–femoral pulse wave velocity is independently associated with endothelial dysfunction [32] and that LA is a marker of dysfunctional endothelium at the kidney level [33]. Finally, in normotensive individuals without DM, AER levels below the threshold for microalbuminuria predicted development of hypertension [34]. In our analysis, the association of LA with systolic BP or PP levels might have been masked by the strong correlation of higher AER with age and also by its relation with anti-hypertensive treatments that, in agreement with the position of the ROADMAP investigators who observed a correlation with the use of amlodipine [15], may be a confounding by indication. Interestingly, our analysis, at variance with the ROADMAP study [15], confirms and extends to the normoalbuminuric range previous data obtained in both T1DM [35] and T2DM [36] showing an association of albuminuria with family history of hypertension, independently of several confounders.

Another strong correlate of LA was smoking habit, though such association was found in males, but not in females. Our data are consistent with previous results in the general population from the Prevention of End Stage Renal

Table 3 Independent covariates of LA in the whole cohort and in subjects without CKD[a]

	All subjects (n = 11,538)			No CKD subjects (n = 10,055)		
	OR	95 % CI	P	OR	95 % CI	P
Gender, male	1.238	1.070–1.432	0.004	1.244	1.064–1.455	0.006
Age, ×1 year	1.018	1.014–1.022	<0.0001	1.018	1.013–1.022	<0.0001
Family history of diabetes	–	–	–	–	–	–
Family history of hypertension	1.325	1.207–1.455	<0.0001	1.346	1.220–1.486	<0.0001
Family history of CVD	0.891	0.792–1.003	0.057	–	–	–
Smoking habits			<0.0001			<0.0001
No smokers	1.0			1.0		
Former smokers	1.158	1.058–1.267	0.001	1.182	1.072–1.302	<0.001
Current smokers	1.237	1.106–1.384	<0.0001	1.273	1.132–1.432	<0.0001
Duration of diabetes, x1 year	–	–	–	–	–	–
HbA_{1c}, ×1 %	1.062	1.033–1.093	<0.0001	1.064	1.032–1.097	<0.0001
Lifestyle	1.0			1.0		
OHA	1.312	1.175–1.464	<0.0001	1.286	1.145–1.444	<0.0001
Insulin + OHA	1.334	1.126–1.581	0.001	1.268	1.056–1.522	0.011
Insulin	1.495	1.288–1.734	<0.0001	1.482	1.259–1.744	<0.0001
BMI, ×1 kg/m^2	–	–	–	–	–	–
Waist circumference, ×1 cm	1.050	0.996–1.106	0.070	1.055	0.997–1.115	0.062
Triglycerides, ×0.01 mmol/L	1.001	1.000–1.001	0.011	1.001	1.000–1.001	0.054
Total cholesterol, ×0.03 mmol/L	–	–	–	1.001	1.000–1.002	0.041
HDL cholesterol, ×0.03 mmol/L	–	–	–	–	–	–
Lipid-lowering treatment	–	–	–	–	–	–
Systolic BP, ×1 mmHg	–	–	–	–	–	–
Diastolic BP, ×1 mmHg	1.014	1.010–1.018	<0.0001	1.015	1.010–1.019	<0.0001
RAS blockers	1.073	0.992–1.160	0.077	1.073	0.987–1.167	0.091
DHP Ca-channel blockers	1.171	1.053–1.302	0.004	1.175	1.047–1.319	0.006
DR			0.072			0.044
No	1.0			1.0		
Non-advanced	1.141	1.010–1.288	0.035	1.174	1.029–1.340	0.017
Advanced	1.095	0.942–1.271	0.237	1.095	0.928–1.293	0.282

Continuous or categorical variables not entering in regression: serum creatinine, treatment with antihypertensive drugs, treatment with lipid-lowering agents, obesity, and metabolic syndrome

In an alternative model, central obesity (OR 1.135, 95 % CI 1.030–1.250, P = 0.010, in the whole cohort; OR 0.121, 95 % CI 1.014–1.257, P = 0.019, in subjects without CKD) enters instead of waist circumference, with no effect on other covariates

LA low albuminuria, *CKD* chronic kidney disease, *OR* odds ratio, *CI* confidence interval, *CVD* cardiovascular disease, *HbA_{1c}* haemoglobin A_{1c}, *OHA* oral hypoglycaemic agent, *BP* blood pressure, *RAS* renin–angiotensin system, *DHP* dihydropyridine, *DR* diabetic retinopathy

[a] Binary logistic regression analysis with backward conditional entering of independent variables

and Vascular Disease Study, in which smoking was associated with albuminuria at a concentration of ≥5.1 mg/L [37], as well as with those in the T2DM cohort from the ROADMAP study, in which higher ACR levels were observed among smokers, more so in males than in females [15].

Finally, our study provided further insights into the association of LA with central obesity and dyslipidemia, which cluster with impaired glucose regulation and hypertension in the MS. In fact, we found correlations of LA with waist circumference and central obesity (especially in males) and, to a lesser extent, with triglycerides (only in females), but not with the MS. These results are consistent with those from the ROADMAP study, except for the lack of association with the MS [15].

It is important to highlight the fact that most of the independent correlates of LA identified by our analysis were previously found to predict (or to correlate with) the development and progression/regression of microalbuminuria in patients with T1DM and/or T2DM and also in the general population. In fact, intensive treatment was found to reduce the risk of microalbuminuria in both T1DM [9,

Table 4 Independent covariates of LA in the whole cohort and in subjects without CKD by gender[a]

	All subjects (n = 11,538)						No CKD subjects (n = 10,055)					
	Males (n = 6102)			Females (n = 5436)			Males (n = 5509)			Females (n = 4546)		
	OR	95 % CI	P	OR	95 % CI	P	OR	95 % CI	P	OR	95 % CI	P
Age, x 1 year	1.015	1.010–1.021	<0.0001	1.018	1.013–1.024	<0.0001	1.015	1.010–1.021	<0.0001	1.018	1.012–1.024	<0.0001
Family history of diabetes	–	–	–	–	–	–	–	–	–	1.115	0.981–1.266	0.095
Family history of hypertension	1.227	1.073–1.403	0.003	1.399	1.232–1.590	<0.0001	1.244	1.082–1.432	0.002	1.406	1.226–1.612	<0.0001
Family history of CVD	0.828	0.697–0.983	0.031	–	–	–	0.837	0.700–1.002	0.053	–	–	–
Smoking habits			<0.0001	–	–	–			<0.0001	–	–	–
No smokers	1.0			–	–	–	1.0			–	–	–
Former smokers	1.246	1.112–1.397	<0.0001	–	–	–	1.261	1.117–1.423	<0.0001	–	–	–
Current smokers	1.365	1.183–1.575	<0.0001	–	–	–	1.408	1.213–1.633	<0.0001	–	–	–
Duration of diabetes, ×1 year	–	–	–	–	–	–	–	–	–	–	–	–
HbA_{1c}, ×1 %	1.111	1.068–1.156	<0.0001	–	–	–	1.110	1.064–1.158	<0.0001	–	–	–
Glucose-lowering treatment			0.011			<0.0001			0.059			<0.0001
Lifestyle	1.0			1.0			1.0			1.0		
OHA	1.233	1.067–1.424	0.004	1.485	1.252–1.760	<0.0001	1.175	1.012–1.364	0.035	1.494	1.243–1.796	<0.0001
Insulin + OHA	1.176	0.931–1.485	0.175	1.649	1.297–2.095	<0.0001	1.128	0.883–1.443	0.335	1.555	1.195–2.023	0.001
Insulin	1.362	1.116–1.660	0.002	1.819	1.463–2.262	<0.0001	1.326	1.071–1.642	0.010	1.851	1.453–2.358	<0.0001
BMI, ×1 kg/m^2	–	–	–	–	–	–	–	–	–	–	–	–
Waist circumference, ×1 cm	1.007	1.001–1.012	0.017	–	–	–	1.008	1.002–1.014	0.010	–	–	–
Triglycerides, ×0.01 mmol/L	–	–	–	1.001	1.000–1.002	0.010	–	–	–	1.001	1.000–1.002	0.007
Total cholesterol, ×0.03 mmol/L	1.002	1.000–1.003	0.024	–	–	–	1.002	1.001–1.004	0.009	–	–	–
HDL cholesterol, ×0.03 mmol/L	–	–	–	–	–	–	–	–	–	–	–	–
Lipid-lowering treatment	–	–	–	–	–	–	–	–	–	–	–	–
Systolic BP, ×1 mmHg	–	–	–	1.004	1.000–1.007	0.043	–	–	–	–	–	–
Diastolic BP, ×1 mmHg	1.011	1.006–1.017	<0.0001	1.013	1.007–1.020	<0.0001	1.013	1.007–1.019	<0.0001	1.016	1.010–1.023	<0.0001
RAS blockers	1.178	1.058–1.311	0.003	–	–	–	1.157	1.033–1.295	0.012	–	–	–
DHP Ca-channel blockers	1.329	1.140–1.550	<0.0001	–	–	–	1.374	1.165–1.621	<0.0001	–	–	–
DR	–	–	–			0.083	–	–	–			0.090
No	–	–	–	1.0			–	–	–	1.0		
Non-advanced	–	–	–	1.210	1.014–1.443	0.034	–	–	–	1.229	1.009–1.496	0.040
Advanced	–	–	–	1.114	0.902–1.374	0.316	–	–	–	1.138	0.895–1.447	0.293

Other continuous or categorical variables not entering in regression: serum creatinine, treatment with anti-hypertensive drugs, treatment with lipid-lowering agents, obesity, and metabolic syndrome

In an alternative model, in males only, central obesity (OR 1.125, 95 % CI 1.012–1.251, P = 0.029, in the whole cohort; OR 1.107. 95 % CI 0.987–1.235, P = 0.074, in subjects without CKD) enters instead of waist circumference, with no effect on other covariates

LA low albuminuria, *CKD* chronic kidney disease, *OR* odds ratio, *CI* confidence interval, *CVD* cardiovascular disease, *HbA_{1c}* haemoglobin A_{1c}, *OHA* oral hypoglycaemic agent, *BP* blood pressure, *RAS* renin–angiotensin system, *DHP* dihydropyridine, *DR* diabetic retinopathy

[a] Binary logistic regression analysis with backward conditional entering of independent variables

10] and T2DM [14, 38]. In particular, in patients with T2DM from the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation trial, intensive glucose control significantly reduced progression of albuminuria by 10 % and increased its regression by 15 % [39] and similar data were obtained in subjects with T1DM from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort [40]. Moreover, HbA_{1c} was an independent predictor of incident microalbuminuria, together with age in patients with T1DM [9] and T2DM [14]. Finally, previous studies showed that (a) waist circumference and central obesity predict albuminuria in both T1DM [9] and T2DM [14] and, at least in males, in the general population [41]; (b) lipid levels are associated with microalbuminuria in both T1DM [19] and T2DM [14, 42]; and (c) the MS is not an independent predictor of AER increase in surveys from the general population [41], though it is independently associated with microalbuminuria in patients with T2DM [43].

The strengths of our study include the large size of the cohort, the completeness of data, and the analysis of a contemporary and real-life data set. Furthermore, as we excluded only subjects on dialysis, we are confident that our cohort may be representative of the T2DM population with normoalbuminuria. The main limitation is the cross-sectional design which does not allow to assess causality and to exclude reverse causality or bidirectional relationships between variables. Potential limitations concerning non-centralized measurements of albuminuria and creatinine and the use of funduscopy in the assessment of DR have been extensively addressed in previous reports [8, 20, 21, 24]. Another limitation might be the lack of data about other potentially relevant covariates of raised albuminuria such as uric acid, haemoglobin, inflammatory markers, surrogate measures of insulin sensitivity, and family history of nephropathy.

In conclusion, our data suggest that multiple risk factors are independent correlates of higher AER levels within the normoalbuminuric range, including glycemic control, BP levels, and other components of the MS as well as age and smoking habits. These factors, most of which are potentially modifiable by intervention, recapitulate those previously associated with development and progression/regression of microalbuminuria. Therefore, therapeutic intervention targeted to these factors might help to reduce high levels of albuminuria within the normoalbuminuric range and possibly the increased risk of adverse CVD and renal outcomes associated with them.

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Compliance with Ethical Standards

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Conflict of interest The authors declare no relevant conflict of interest to disclose.

Ethical standard The study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. The protocol was approved by the locally appointed ethics committees, and participants gave informed consent.

Human and Animal Rights disclosure All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent disclosure Informed consent was obtained from all patients for being included in the study.

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