



Impact of albuminuria on early-onset type 2 diabetes mellitus: a nationwide population-based study

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Background: Early-onset diabetes mellitus has a significant lifetime burden and is associated with higher morbidity and mortality. Since insulin resistance is one of the mechanisms of podocyte injury, we aimed to evaluate the effect of albuminuria on newly developed early-onset type 2 diabetes mellitus (T2DM).

Methods: We screened 6,891,399 subjects aged ≥ 20 and < 40 years without a history of prediabetes or diabetes from the Korean National Health Insurance Service database between 2009 and 2012. A multivariate Cox proportional hazard model was used to identify the impact of albuminuria on early-onset T2DM.

Results: Among a total of 5,383,779 subjects, 62,148 subjects (1.2%) developed early-onset diabetes over 7.3 ± 1.2 years. Albuminuria was significantly associated with early-onset T2DM (adjusted hazard ratio [aHR], 1.62; 95% confidence interval [CI], 1.55–1.70) after adjustment for age, sex, anthropometric data, physical exercise status, serum glucose, and total cholesterol. The risk of early-onset T2DM increased more in subjects with more components of metabolic syndrome (MetS). Among each component of MetS, hypertriglyceridemia was prominently associated with early-onset T2DM (aHR, 2.02; 95% CI, 1.81–2.25) in subjects with albuminuria.

Conclusion: Dipstick albuminuria was significantly associated with early-onset T2DM in young adult populations. Close monitoring of albuminuria is warranted for disease risk modification, especially in subjects with MetS.

Keywords: Albuminuria, Dipstick urinalysis, Metabolic syndrome, Type 2 diabetes mellitus, Early-onset

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Introduction

Type 2 diabetes mellitus (T2DM) in young adults has recently increased worldwide. Even though prevalence varies widely by region and ethnicity, increasing trends have been commonly observed. Early-onset T2DM, defined as the onset of diabetes before the age of 40 years, is clinically crucial because of the increased lifetime burden of higher morbidity and mortality compared to that in late-onset diabetic patients [1–3]. Furthermore, as a multisystemic disease, individuals with early-onset T2DM usually suffer from a higher risk of complications and a higher socioeconomic burden [4].

Albuminuria is a well-established marker representing kidney damage. Additionally, albuminuria is a marker of endothelial dysfunction, which leads to the increased transcapillary escape of albumin, triggering an inflammatory reaction in the vessel wall [5]. In this regard, even a small amount of urinary albumin excretion represents kidney damage and is also used as a diagnostic criterion of diabetic kidney disease [6,7]. Above all, the prevalence of microalbuminuria in early-onset T2DM is linked to the high rate of progression to macroalbuminuria and macrovascular complications [8–10].

It has been reported that local insulin-receptor signaling occurs in the podocytes of the kidney, which is one of the target organs of insulin action [11,12]. Insulin resistance, the primary pathophysiological process of diabetes, correlates with the function of cells such as podocytes and endothelial cells that make up the glomerular filtration barrier [13]. Moreover, insulin resistance deteriorated more in individuals with early-onset diabetes than in individuals with late-onset diabetes [14]. Therefore, albuminuria has a role as a predisposing factor for the development of diabetes, especially for young adult populations. A previous cross-sectional study revealed that microalbuminuria was closely correlated with metabolic syndrome (MetS) [15]. In addition, microalbuminuria significantly increased the risk of T2DM in subjects with metabolic diseases such as MetS or impaired glucose tolerance [2,16].

Considering the significance of lifetime disease burden in the young population, we aimed to evaluate the impact of albuminuria as a predictive factor for the early diagnosis of T2DM in this special population. Additionally, we tried to evaluate the impact of the components of MetS on the

development of early-onset T2DM in this study.

Methods

Ethical considerations

This study complied with the Declaration of Helsinki. The Institutional Review Board of Seoul National University Hospital approved this study (No. E-2107-186-1237). The attending government organization approved this study using the data from the National Health Insurance Service (NHIS; No. NHIS-2021-1-592). The subject data were anonymized and de-identified for the analysis, so the requirement for informed consent was waived.

Study population and clinical parameters

We extracted data from populations aged ≥ 20 and < 40 years who underwent health check-ups during 2009 and 2012. Among all subjects, we excluded subjects with diabetes or a history of prediabetes. The subjects were divided into subgroups according to age of 30 years, sex, the number of components of MetS, and the status of each component of MetS.

Data acquisition and definitions

All data, including anthropometric data, laboratory results, and diagnostic information, were obtained from the Korean NHIS database. Exposure was one or more instances of the presence of albuminuria $\geq 1+$ in dipstick urinalysis in health examination results. The development of diabetes or prediabetes during follow-up periods from 2010 to 2018 was regarded as a primary outcome. Diabetes was defined by the diagnostic codes E11 to E14 based on the 10th revision of the International Classification of Diseases (ICD-10) code, oral hypoglycemic agent use or insulin prescription, and fasting glucose of ≥ 126 mg/dL. Prediabetes was defined by the diagnostic code R730 and fasting glucose of ≥ 100 and < 126 mg/dL. MetS was defined when three or more of the following components were present: increased waist circumference (≥ 90 cm for male and ≥ 80 cm for female); elevated triglyceride level (≥ 150 mg/dL) or use of a relevant drug; reduced high-density lipoprotein cholesterol level (< 40 mg/dL for male and 50 mg/dL for female) or use

of a relevant drug; and elevated blood pressure (systolic, ≥ 130 mmHg and/or diastolic, ≥ 80 mmHg) or use of antihypertensive medication. According to the inclusion criteria, no subject showed an increased fasting glucose level of ≥ 100 mg/dL or the use of an antidiabetic drug. Chronic kidney disease (CKD) was defined when the estimated glomerular filtration rate was under 60 mL/min per 1.73 m², calculated with the Modification of Diet in Renal Disease equation. Dyslipidemia was defined with the ICD-10 diagnostic code, E78 and a history of lipid-lowering drug use or a total serum cholesterol concentration of ≥ 240 mg/dL in the health examination results.

Statistical analysis

All continuous variables are presented as the mean with standard deviation. Categorical variables are shown as a number of subjects with percentages. We used the Student t test and the chi-square test to compare the two groups. Two-sided p-values were derived, and the significance level was set at 0.05. We used the Cox proportional hazards regression model for risk assessment for the development of diabetes or prediabetes. We adjusted the following variables: age, sex, income status, residence, exercise, smoking status, alcohol consumption status, body mass index (BMI), waist circumference, systolic blood pressure, serum glucose, total cholesterol, and comorbidities, including hypertension and dyslipidemia. The incidence rate was calculated by the number of events per 1,000 person-years. The SAS 9.4 program (SAS Institute) was used for statistical analysis.

Results

Study populations

A total of 5,383,779 subjects were finally included in the analysis ([Supplementary Fig. 1](#), available online). In the comparison of subjects according to the presence of albuminuria, subjects with albuminuria showed more healthy characteristics in anthropometric data such as BMI and waist circumferences compared to the subjects without albuminuria. However, the prevalence of comorbidities such as hypertension, dyslipidemia, and CKD was higher in subjects with albuminuria. A comparison of the baseline

characteristics is shown in [Table 1](#).

Impact of albuminuria on the development of early-onset type 2 diabetes

A total of 62,148 subjects (1.2%) were diagnosed with diabetes during 87.8 ± 13.9 months of follow-up. Albuminuria was significantly associated with early-onset T2DM development ([Fig. 1](#)). The significance was maintained even after adjustment for age, sex, socioeconomic status, comorbidities, and laboratory results ([Table 2](#)). Further sensitivity analysis had been performed among the subjects who were aged ≥ 20 and < 40 years, at the time of the disease development. Albuminuria was significantly associated with early-onset T2DM (adjusted hazard ratio [aHR], 1.63; 95% confidence interval [CI], 1.54–1.74) and the results were consistent after the multivariate adjustments ([Supplementary Table 1](#), available online). The impact of albuminuria on the increased development of early-onset T2DM was more prominent in males (HR, 2.60; 95% CI, 2.47–2.74) than in females (HR, 1.71; 95% CI, 1.56–1.88) ([Supplementary Table 2](#), available online). According to MetS status, albuminuria was significantly associated with risk of early-onset T2DM in subjects with the same number of MetS components ([Table 3](#)). Moreover, the impact of albuminuria was prominent in subjects with ≥ 3 MetS components (aHR, 1.74; 95% CI, 1.63–1.87) after adjustment for such variables ([Table 3](#)).

Impact of exposure duration of albuminuria on the development of early-onset type 2 diabetes mellitus

Among 2,730,791 subjects who underwent two or more health exams, 30,428 and 5,224 subjects showed new-onset and persistent albuminuria, respectively. The interval duration between the first and second exams was 1.69 ± 0.51 years. According to the exposure duration, persistent exposure to albuminuria showed the highest association for the development of early-onset T2DM (aHR, 2.49; 95% CI, 2.12–2.92). Moreover, new-onset albuminuria was significantly associated with early-onset T2DM (aHR, 1.61; 95% CI, 1.45–1.79) ([Supplementary Table 3](#), available online).

Table 1. Baseline characteristics

Characteristic	Total	Albuminuria–	Albuminuria+	p-value
No. of patients	5,383,779	5,302,542	81,237	
Age (yr)	30.6 ± 5.0	30.8 ± 5.0	30.1 ± 5.1	<0.001
20–30	2,406,444 (44.7)	2,366,678 (44.6)	39,766 (49.0)	<0.001
≥30	2,977,335 (55.3)	2,935,864 (55.4)	41,471 (51.0)	
Male sex	3,033,023 (56.3)	2,995,476 (56.5)	37,547 (46.2)	<0.001
Smoke				<0.001
Non	3,079,319 (57.2)	3,028,238 (57.1)	51,081 (62.9)	
Ex	531,395 (9.9)	524,143 (9.9)	7,252 (8.9)	
Current	1,773,065 (32.9)	1,750,161 (33.0)	22,904 (28.2)	
Drink				<0.001
Non	2,094,152 (38.9)	2,060,371 (38.9)	33,781 (41.6)	
Mild	2,859,855 (53.1)	2,818,574 (53.1)	41,281 (50.8)	
Heavy	429,772 (8.0)	423,597 (8.0)	6,175 (7.6)	
Regular exercise	685,015 (12.7)	674,105 (12.7)	10,910 (13.4)	<0.001
Body mass index (kg/m ²)	22.7 ± 3.47	22.7 ± 3.5	22.6 ± 4.0	<0.001
<18.5	449,096 (8.3)	438,819 (8.3)	10,277 (12.7)	
<23	2,656,753 (49.3)	2,618,518 (49.4)	38,235 (47.1)	
<25	1,016,207 (18.9)	1,003,585 (18.9)	12,622 (15.5)	
<30	1,081,043 (20.1)	1,065,410 (20.1)	15,633 (19.2)	
≥30	180,680 (3.4)	176,210 (3.3)	4,470 (5.5)	
Waist circumference (cm)	76.7 ± 9.75	76.7 ± 9.7	75.9 ± 11.1	<0.001
SBP (mmHg)	116.7 ± 12.8	116.7 ± 12.8	117.4 ± 15.1	<0.001
DBP (mmHg)	73.1 ± 9.2	73.1 ± 9.2	74.0 ± 10.8	<0.001
Income low, ≤25%	1,147,987 (21.3)	1,129,789 (21.3)	18,198 (22.4)	<0.001
Place, urban	2,587,026 (48.1)	2,545,249 (48.0)	41,777 (51.4)	<0.001
Hypertension	316,313 (5.9)	306,735 (5.8)	9,578 (11.8)	<0.001
Dyslipidemia	304,907 (5.7)	297,568 (5.6)	7,339 (9.0)	<0.001
Chronic kidney disease	141,149 (2.6)	137,255 (2.6)	3,894 (4.8)	<0.001
Metabolic syndrome	274,563 (5.1)	268,005 (5.1)	6,558 (8.1)	<0.001
Total cholesterol (mg/dL)	182.6 ± 32.8	182.5 ± 32.8	186.1 ± 36.2	<0.001
HDL-C (mg/dL)	57.8 ± 22.2	57.8 ± 22.2	59.1 ± 18.7	<0.001
LDL-C (mg/dL)	103.7 ± 33.9	103.6 ± 33.9	105.4 ± 33.6	<0.001
Triglyceride (mg/dL)	91.9 (91.8–91.9)	91.9 (91.9–91.9)	89.5 (89.2–89.9)	<0.001
Glucose (mg/dL)	86.3 ± 7.8	86.3 ± 7.8	86.0 ± 8.0	<0.001
GFR (mL/min/1.73 m ²)	96.7 ± 51.3	96.7 ± 51.4	93.0 ± 39.5	<0.001
Follow-up (mo)	87.8 ± 13.9	87.8 ± 13.9	87.1 ± 14.8	<0.001

Data are expressed as number only, mean ± standard deviation, number (%), or geometric mean (95% confidence interval).

DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

Impact of metabolic syndrome on the development of early-onset type 2 diabetes mellitus

In subjects with albuminuria, the number of MetS components also increased the risk of early-onset T2DM ([Supplementary Fig. 2](#), available online). Subjects who developed

early-onset T2DM showed a higher prevalence for each component of MetS compared to the subjects who didn't develop diabetes ([Supplementary Table 4](#), available online). Compared to the subjects without any components of MetS, the risk of diabetes was 5.33 times (95% CI, 4.38–6.50) increased in subjects with ≥3 MetS components ([Fig.](#)

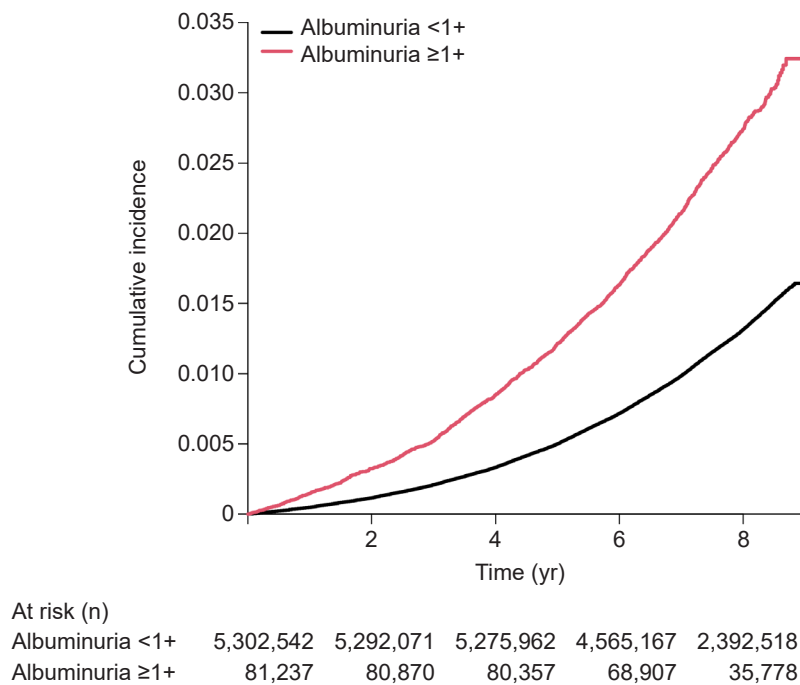


Figure 1. Cumulative risk of early-onset type 2 diabetes mellitus according to the presence of albuminuria.

Table 2. Risk of albuminuria on the development of early-onset type 2 diabetes mellitus

Albuminuria	No. of subjects	No. of events	IR	Model 1		Model 2		Model 3		Model 4	
				HR (95% CI)	p-value	aHR (95% CI)	p-value	aHR (95% CI)	p-value	aHR (95% CI)	p-value
<1+	5,302,542	60,208	1.55	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
≥1+	81,237	1,940	3.29	2.13 (2.04–2.23)	<0.001	2.33 (2.23–2.44)	<0.001	2.15 (2.05–2.25)	<0.001	1.62 (1.55–1.70)	<0.001

Model 1, non-adjusted; Model 2, adjusted with age, sex; Model 3, adjusted with variables in model 2 and income status, residual place, exercise, smoking, drinking, body mass index; Model 4, adjusted with variables in model 3 and hypertension, dyslipidemia, waist circumference, systolic blood pressure, serum glucose, total cholesterol.

aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; IR, incidence rate per 1,000 persons.

2). Among each component of MetS, abnormalities in lipid profiles increased the risk of early-onset T2DM more than other components of MetS (Fig. 2).

Discussion

In this study, we found that albuminuria was significantly associated with early-onset T2DM irrespective of age, sex, and the presence of MetS. The risk of early-onset T2DM was more prominent in subjects with a higher number of MetS components or more prolonged exposure to albu-

minuria. Among subjects with albuminuria, all components of MetS were associated with early-onset T2DM, but problems with lipid profiles conspicuously increased the risk of T2DM.

The onset age of diabetes is a critical indicator of prognosis [2]. Unlike traditional diabetes that develops in elderly individuals, early-onset T2DM has a considerably high risk of complications and mortality and enormous socioeconomic burdens [4]. These effects could be related to the duration of diabetes, which significantly increases the risk of microvascular and macrovascular events and death [17].

Table 3. Risk of albuminuria on the development of early-onset type 2 diabetes mellitus according to the number of metabolic syndrome components (MetS)

No. of MetS (albuminuria)	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	p-value	aHR (95% CI)	p-value	aHR (95% CI)	p-value	aHR (95% CI)	p-value
0 (<1+)	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	0.108
0 (≥1+)	1.29 (1.13–1.48)		1.38 (1.20–1.58)		1.43 (1.24–1.64)		1.41 (1.23–1.62)	
1–2 (<1+)	Reference		Reference		Reference		Reference	
1–2 (≥1+)	1.86 (1.74–1.99)		1.92 (1.80–2.06)		1.85 (1.73–1.98)		1.65 (1.54–1.76)	
≥3 (<1+)	Reference		Reference		Reference		Reference	
≥3 (≥1+)	2.18 (2.04–2.34)		2.17 (2.02–2.32)		2.01 (1.88–2.16)		1.74 (1.63–1.87)	

Model 1, non-adjusted; Model 2, adjusted with age, sex; Model 3, adjusted with variables in model 2 and income status, residual place, exercise, smoking, drinking, body mass index; Model 4, adjusted with variables in model 3 and hypertension, dyslipidemia, waist circumference, systolic blood pressure, serum glucose, total cholesterol.
aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio.

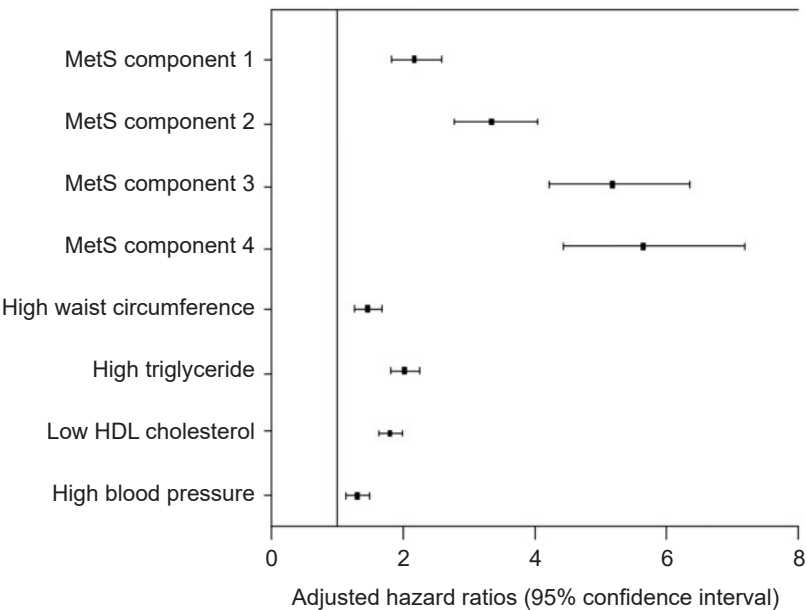


Figure 2. Risk of early-onset type 2 diabetes mellitus according to the number of MetS components and the status of each MetS component. For the analyses of the number of MetS components, subjects without any component of MetS were regarded as a reference. For the analyses of each component of MetS, subjects with normal values were regarded as a reference group. The results were adjusted for age, sex, income status, place of residence, exercise, smoking, alcohol consumption, body mass index, hypertension, dyslipidemia, waist circumference, systolic blood pressure, serum glucose, and total cholesterol.
HDL, high-density lipoprotein; MetS, metabolic syndrome.

Moreover, early-onset T2DM is related to a lower threshold for insulin resistance; early-onset T2DM was also associated with hyperglycemia, obesity, MetS, and cardiovascular disease (CVD) [18]. Therefore, early diagnosis and management of young-onset diabetes are crucial to improve prognosis.

The hazard of the presence of albuminuria in diabetic patients is well-established. However, the role and effect of albuminuria as a diagnostic factor have not yet been well evaluated. Among many factors related to the pathophysiology of albuminuria, podocyte injury plays a critical role irrespective of diabetes. Especially as an insulin

sensitizer, deficiency of insulin receptors in podocytes is closely linked to the pathologic change similar to diabetic nephropathy even in the absence of diabetes [12]. Likewise, dysregulated insulin responses in podocytes led to podocyte damage and contributed to the development of albuminuria [19].

In addition, albuminuria plays a role as a marker of inflammation and oxidative stress [20]. Albuminuria is a well-recognized sign of kidney disease and an independent risk factor for the progression of kidney dysfunction [21,22]. Inflammation and oxidative stress are also linked to insulin resistance [23]. In this study, we could not determine the state of insulin resistance. Nevertheless, we suggest that insulin resistance, as a pathogenic driver of such metabolic diseases, including obesity, MetS, and diabetes, is closely linked to the presence of albuminuria, even in an euglycemic state. Thus, as an early marker representing the development of diabetes, albuminuria may have a role as a relative factor involved in the early onset of the development of diabetes and may have an impact on the progression of comorbidities of diabetes.

Albuminuria is an independent risk factor for adverse cardiovascular events and an increase in all-cause mortality [24]. Moreover, previous reports demonstrated that persistent albuminuria was associated with an increased risk of CVDs and overall mortality [25,26]. Albuminuria is an indicator of damage to the glomerular filtration barrier [27]. Increased amounts of albuminuria may dysregulate the glomerular pores and aggravate the damage of glomerular filtration barriers [28]. Regarding the deleterious effects on glomerular structures, persistently exposed albuminuria may have contributed to organ damage and led to the development of systemic diseases. In addition to the presence of albuminuria, persistently detected albuminuria in repeated exams significantly increased the risk of diabetes development in this study. To minimize the harmful impact of persistent albuminuria on adverse outcomes, repeated measurements and continual follow-up examinations of albuminuria are essential.

MetS is a major risk factor for the development of diabetes. Indeed, diabetic patients showed a higher prevalence of all components of MetS. The impact of albuminuria on newly developed early-onset T2DM was incrementally increased according to the number of MetS components in this study. This impact of MetS status was more prominent

in subjects with albuminuria. Among subjects with albuminuria, dyslipidemia, including higher triglyceride and lower high-density lipoprotein cholesterol levels, resulted in an increased risk of early-onset T2DM. Considering the enormous effort to identify manageable factors to reduce the risk of the development of CKD and CVD, the main comorbidities related to diabetes, this information that all components of MetS are manageable could be valuable.

Proper detection of albuminuria is critical for reducing private medical and socioeconomic burdens after a diagnosis of T2DM. As a result, annual screening for albuminuria is usually recommended in the guidelines [29]. Likewise, screening for albuminuria to predict diabetes could be suggested to reduce these burdens in the general population. Dipstick albuminuria is a simple and easily accessible tool to be used in primary clinics. Therefore, it may provide the opportunity for clinicians to identify the young population at risk of T2DM and improve the prognosis among young patients through early intervention. Considering the cost-related factors of lifelong diabetes in the young population, albuminuria in the young population, especially those with MetS, should be cautiously monitored. From the present study, we expect to detect the population at risk of early-onset T2DM to intervene in advance.

This study is valuable in showing the significance of albuminuria to be used as a diagnostic marker to assist early diagnosis of new-onset diabetes, especially early-onset T2DM among the young population. Nevertheless, there are several concerns to be discussed. First, this study was performed based on an observational cohort study; it was difficult to identify the causal relationship between albuminuria and new-onset T2DM. This study could be background epidemiological evidence to perform a further investigation to reveal the pathophysiological evidence of albuminuria as a predisposing risk factor for the development of diabetes is necessary. Although the prevalence of young-onset diabetes was widely different according to region and ethnicity, this study included only single-nation populations. Third, we used dipstick urinalysis to measure albuminuria rather than quantitative methods. This method could not indicate the impact of the exact amount of albuminuria, but it was a more convenient and inexpensive approach as a screening tool. Moreover, prediabetes was defined with the diagnostic code and the definition of

impaired fasting glucose. Due to the absence of the results of the oral glucose tolerance test, some subjects with impaired glucose tolerance without the diagnostic code may have been excluded.

Albuminuria, detected using dipstick urinalysis, is an excellent parameter to assist risk stratification and early diagnosis of new-onset T2DM in young populations. Given the longer life expectancy of these special populations and the greater disease burden of T2DM, physicians need to consider that screening of albuminuria would be a guaranteed method to obtain a chance for early diagnosis of the disease and to have an opportunity to intervene earlier.

Conflicts of interest

Seungyeup Han is the Associate Editor of *Kidney Research and Clinical Practice* and was not involved in the review process of this article. The author has no other conflicts of interest to declare.

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Data sharing statement

The data presented in this study are available on request from the corresponding author.

Authors' contributions

Conceptualization, Methodology: SL, YK
Investigation, Formal analysis, Data curation: SC, GNN, JC, SGK, MK, HH, SL, KH
Resources: EK, SP, JHP, WYP, KJ, SH, KWJ
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Writing - review & editing: EK, SP, JHP, WYP, KJ, SH, KWJ
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