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ORIGINAL ARTICLE

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The retinopathy-derived HbA1c threshold of 6.5% for type 2 diabetes also captures the risk of diabetic nephropathy in NHANES

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Abstract

Aim: To determine if an HbA1c diagnostic threshold of less than 6.5% (<48 mmol/mol) could be identified based on a urinary albumin-creatinine ratio (UACR) of 30 mg/g or higher in subjects not known to have diabetes.

Methods: A UACR was measured for 20 158 participants in the 2011-2018 nationally representative cross-sectional National Health and Nutrition Examination Surveys (NHANES; cycles 7-10 inclusive).

Results: There was a significant trend for an increasing risk with a UACR of 30 mg/g or higher across increasing HbA1c categories ($P < .0001$). This trend was mainly attributable to the high prevalence of raised UACR in the 7.0% or higher HbA1c subgroup of subjects not previously diagnosed with diabetes. None of the odds ratios in the lower HbA1c subgroups versus the HbA1c subgroup of less than 5.0% reached significance. There were racial/ethnic differences in UACR risk ($P < .0001$), with White and Black subjects exhibiting little increased risk (vs. HbA1c <5.0%) until they reached an HbA1c of 7.0%, while Asian and Hispanic subjects showed some increased, but non-significant, risks at lower HbA1c levels. Maximizing the area under receiver operating characteristic curves from logistic regressions predicted an ideal HbA1c threshold of 5.8%, but there was little variation in area from 5.5% to 7.0%.

Conclusion: A clinically useful diagnostic threshold below 6.5% for HbA1c for elevated UACR risk was not identified, with an increased risk only obvious at an HbA1c of 7.0% or higher. Thus, the retinopathy-derived HbA1c threshold of 6.5% also captures the risk of diabetic nephropathy in NHANES.

KEYWORDS

HbA1c, NHANES, type 2 diabetes, urinary albumin-creatinine ratio

1 | INTRODUCTION

The magnitude of diabetes prevalence has reached pandemic proportions, with 8.8% of the global adult population affected, a figure equating to 424.9 million adults. Current projections indicate that, by 2045, 628.6 million will be affected, equating to 10% of the global adult population.¹ Type 2 diabetes (T2D) constitutes the overwhelming majority (90%-95%) of diabetes cases and is characterized by inadequate secretion of insulin from pancreatic beta cells as a result of the combined effects of a deficit of functional beta cells and peripheral insulin resistance. The precise criteria used to diagnose diabetes have been a source of ongoing debate in terms of what to measure, and what the appropriate diagnostic targets should be; these targets have evolved in response to improvements in knowledge of disease progression together with enhanced analytical methods.

Whilst the diagnostic criteria for diabetes have been established as a practical necessity for diagnosis and management of patients in clinical practice,² on a population basis it is evident that blood glucose exists on a continuum, spanning a range from normoglycaemia to overt diabetes. This issue was addressed in 1997 and again in 2003 by the Expert Committee on Diagnosis and Classification of Diabetes Mellitus, where they recognized a group of individuals in whom glucose levels were elevated above normal but not to the level of frank diabetes^{3,4}; this 'prediabetic' group showed impaired fasting glucose (fasting plasma glucose levels of 100-125 mg/dL [5.6-6.9 mmol/L] and/or impaired glucose tolerance defined as a 2-hour plasma glucose following a 75-g oral glucose tolerance test of 140-199 mg/dL [7.8-11.0 mmol/L]), and these individuals are recognized as being at a high risk of progression to T2D.

HbA1c is a key tool for assessing glycaemic status, and a number of prospective studies have reported a robust relationship between HbA1c and the development of both diabetes and its complications.⁵⁻⁷ Consequently, the International Expert Committee (IEC) put forward the recommendation of an HbA1c level of 6.5% (48 mmol/mol) as the threshold for diabetes diagnosis⁸; notably, their recommendation was predicated upon the probability that individuals with HbA1c levels of 6.5% or more have a markedly increased risk of retinopathy relative to those whose HbA1c falls below that threshold. Endorsed by both the American Diabetes Association (ADA) and the World Health Organization, this recommendation was accepted based solely upon evidence of diabetic retinopathy risk from several key studies,^{3,9-11} without any consideration given to the other diabetic microvascular complications of nephropathy and neuropathy.

However, even at the time, experts voiced concern that an HbA1c threshold of 6.5% (48 mmol/mol) might be too high because diagnosis of diabetes using blood glucose criteria identified more individuals.¹² Subsequent studies have focused upon better delineating the optimal HbA1c threshold based upon all three microvascular diabetic complications^{13,14} and indicate that the current threshold of 6.5% may indeed be too high.

The key aim of this study was to determine if an HbA1c diagnostic threshold could be discerned based upon albuminuria, defined as a urinary albumin-creatinine ratio (UACR) of more than 30 mg/g, in

a large population and, specifically, whether this threshold would be less than 6.5%. The study population was derived from the published National Health and Nutrition Examination Surveys (NHANES) 2011-2018 (cycles 7-10 inclusive).¹⁵

2 | RESEARCH DESIGN AND METHODS

NHANES is a cross-sectional probability sample of the US non-institutionalized population, with both interview and examination components, and has been described elsewhere.¹⁵ During 2011-2018, 39 156 individuals participated in NHANES (data release cycles 7-10), of whom 21 199 adults aged 18 years or older participated in the examination component of NHANES and had urine albumin, urine creatinine and plasma HbA1c measurements. Survey participants were oversampled from different race/Hispanic origin subpopulations. Individuals who reported they were of Hispanic origin were categorized as Hispanic regardless of their race and, for this analysis, Mexican Americans and other Hispanics were combined. Those not of Hispanic origin were categorized into four different groups (non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, and other). The National Center for Health Statistics Research Ethics Review Board approved NHANES.

Subjects with missing body mass index (BMI), HDL-cholesterol, systolic blood pressure (SBP) and current smoking status, or those who had a diabetes diagnosis aged younger than 18 years were excluded, leaving 20 158 subjects for analysis. Abnormal UACRs were defined as 30 mg/g or higher.¹⁶

HbA1c categories were defined using HbA1c of less than 5.0%, 5.0% to less than 5.7%, 5.7% to less than 6.0%, 6.0% to less than 6.5%, 6.5% to less than 7.0%, and 7.0% or higher. An additional HbA1c category was defined as those with diabetes or on antidiabetic treatment regardless of their HbA1c levels. Diabetes was defined by the NHANES question asking if the person had ever been told that he or she had diabetes (other than in pregnancy).

Means, medians and percentages were obtained from Proc SurveyMeans or Proc SurveyFreq (version 9.4; SAS Inc., Cary, NC, USA), using the NHANES-recommended strata, cluster and weight variables from the examination component to correct for the sampling scheme. Logistic regressions for UACRs of 30 mg/g or higher versus those less than 30 mg/g were performed using Proc SurveyLogistic. A domain variable was specified when subsets of the dataset were analysed (e.g. race or diabetes) to preserve the proper study weights. HbA1c category was the independent variable. A test for linear trend of UACR prevalence across HbA1c categories was performed by considering HbA1c category as a continuous variable. To investigate if other variables might confound the HbA1c and UACR relationship, sex, age, race, current smoking status (yes/no), BMI, HDL-cholesterol, LDL-cholesterol, triglycerides, SBP, diastolic blood pressure and examination cycle were initially included in the logistic regression model. Only sex,

age, race, current smoking status and SBP were significantly related to UACR and were kept in the model.

For the threshold analyses, HbA1c was dichotomized at each threshold and used as the independent variable along with the covariates specified above. The HbA1c threshold was moved from 4.7% to 7.0% by 0.1% intervals and odds ratios (ORs) and the area under the receiver operating characteristic curves (AUC) were calculated at each threshold.

3 | RESULTS

The demographics of the dataset are shown in Table 1: 51.3% were female with an average age (standard error [SE]) of 46.9 (0.32) years; 10.5% were known to have diabetes, of whom 84.3% were recorded

to be on treatment, defined as receiving antidiabetic medication, either oral or insulin.

Table S1 depicts those with and those without an elevated UACR by HbA1c category and by diabetes status. The percentage of the sample with a UACR of 30 mg/g or higher was 9.8%. There was a significant trend for an increased prevalence of abnormal UACR as HbA1c increased; this was the case for all subjects ($P < .0001$) as well as those subgroups with ($P < .0001$) and without diabetes ($P < .0001$).

Figure 1 shows the ORs and 95% confidence intervals (CIs) for the probability of a UACR of 30 mg/g or higher in all subjects ($N = 20\,158$) from the 2011-2018 NHANES dataset comparing HbA1c categories with the HbA1c referent category of less than 5.0%. Only the HbA1c group of 7.0% or higher or those on antidiabetic treatment had significantly increased ORs (3.51, 95% CI

TABLE 1 Characteristics of the NHANES 2011-2018 study subjects ($N = 20\,158$)

Study variable	Number of subjects (%) ^a		
Gender (% female)	10 312 (51.3%)		
Diabetes ^b	2802 (10.5%)		
% diabetes patients on Rx	2369 (84.3%)		
Current smoker	3764 (18.3%)		
Hypertensive	7104 (31.9%)		
Albumin-creatinine ratio ≥ 30 mg/g	2502 (9.8%)		
Race/ethnicity ($N = 20\,158$)	Number of subjects (%) ^a		
Mexican American	2838 (8.8%)		
Other Hispanic	2113 (6.3%)		
White	7465 (65.1%)		
Black	4452 (10.9%)		
Asian	2532 (5.3%)		
Other	758 (3.5%)		
Study variable	Number of subjects	Mean (SE) ^a	Median (IQR) ^a
Age (y)	20 158	46.9 (0.32)	46.1 (31.3, 59.9)
BMI (kg/m^2)	20 158	28.6 (0.06)	27.8 (26.7, 31.7)
Age told had diabetes (y)	2573	49.9 (0.36)	49.6 (40.3, 58.9)
Diabetes duration (y)	2573	10.8 (0.23)	8.1 (3.1, 14.9)
HbA1c (%)	20 158	5.6 (0.012)	5.4 (5.1, 5.7)
Urine creatinine (mg/dL)	20 158	122 (1.2)	106 (58, 165)
Urine albumin (mg/L)	20 158	34 (1.7)	7.4 (3.8, 15.2)
Albumin-creatinine ratio (mg/g)	20 158	33 (1.7)	6.8 (4.5, 12.1)
Systolic blood pressure (mmHg)	20 158	122 (0.2)	119 (110, 131)
Diastolic blood pressure (mmHg)	20 158	71 (0.3)	71 (64, 77)
HDL-cholesterol (mg/dL)	20 158	54 (0.3)	51 (42, 62)
Triglycerides (mg/dL)	9565	119 (1.8)	95 (65, 143)
LDL-cholesterol (mg/dL)	9435	112 (0.6)	109 (87, 133)
Fasting glucose (mg/dL)	9730	107 (0.5)	100 (93, 109)

Abbreviations: BMI, body mass index; IQR, interquartile range; Rx, treatment; SE, standard error.

^aMeans, medians and percentages adjusted using the sample weights from NHANES to represent the underlying population.

^bDiabetes defined as ever being told they had diabetes or were currently on antidiabetic medication.

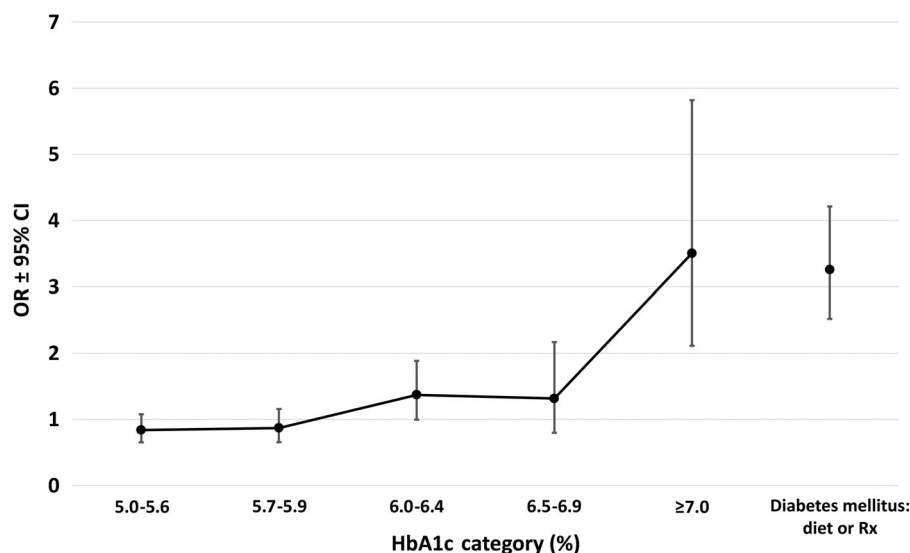


FIGURE 1 Odds ratios (ORs) and 95% confidence intervals (CIs) for urinary albumin creatinine ratios of ≥ 30 versus < 30 mg/g comparing each HbA1c (%) category to the referent category of $< 5.0\%$; $N = 5208$, NHANES 2011-2018. The 'on treatment' group includes all subjects receiving antidiabetic medication regardless of their HbA1c level. ORs were adjusted for age, gender, race, systolic blood pressure and current smoking status. Rx, treatment

2.11-5.82, $P < .0001$ and 3.26, 95% CI 2.52-4.21, $P < .0001$, respectively). The 6.5%-6.9% HbA1c category did not have a significantly greater percentage of elevated UACR than the less than 5.0% group (1.32, 95% CI 0.80-2.17). Age was significantly related to a greater percentage of UACR (OR = 1.010/y, 95% CI 1.005-1.015, $P = .0001$). Race was also significant ($P = .003$) and showed a strong interaction with HbA1c category ($P < .0001$). Women had higher risks than men (OR = 1.30, 95% CI 1.13-1.49, $P = .0002$). Higher SBP was associated with abnormal UACR (OR = 1.026/mmHg, 95% CI 1.023-1.030, $P < .0001$), as was being a current smoker (OR = 1.22, 95% CI 1.03-1.45, $P = .02$).

Figure S1 shows the ORs and 95% CIs of having an elevated UACR of 30 mg/g or higher among untreated non-diabetic subjects ($N = 17\,356$), comparing subjects above and below each dichotomous HbA1c threshold. Each OR was calculated from a logistic regression of high versus low UACR versus the two groups (one above and one below each HbA1c point), adjusted for age, gender, race, SBP and smoking status. An HbA1c threshold of 7.0% or higher versus less than 7.0% clearly defined a high-risk group of subjects with a UACR of 30 mg/g or higher. As the threshold is moved to lower and lower HbA1c levels, the percentage of subjects with high UACR added to the upper HbA1c group becomes smaller and smaller, reducing the OR until the OR is no longer significant below 5.6%. No HbA1c threshold where the OR for a UACR of more than 30 mg/g greatly increased over prior thresholds was apparent, as the trend between 4.7% and 6.5% was approximately linear.

The percentage of subjects with elevated UACR by race is shown in Table S2. From the logistic regression model, the combined Mexican American/Other Hispanic and Black groups had significantly higher percentages of an elevated UACR than the White group (OR = 1.30, 95% CI 1.12-1.50 and OR = 1.20, 95% CI 1.05-1.37, respectively). The non-significant risk of an elevated UACR for the Asian versus the White group was 1.16, 95% CI 0.95-1.41.

Figure 2 shows the lack of a significance for elevated UACR associations with HbA1c from HbA1c categories 5.0%-5.6% through

6.5%-6.9% for all races/ethnic groups. The Black group did not have a significantly elevated risk of high UACR, even in those with an HbA1c of 7.0% or higher, whereas the other three race/ethnic groups showed significance for the HbA1c of 7.0% or higher. An abnormal UACR was apparent for all groups if they had been diagnosed with diabetes. Even though the Hispanic and the Asian groups both showed ORs that were elevated for the 6.5%-6.9% HbA1c category, the CIs were wide, resulting in the OR estimates not being significantly greater than 1.0.

Figure 3 shows a plot of the AUC derived from a logistic regression to predict an elevated UACR as the HbA1c threshold increases by 0.1% from 4.3% to 7.0% in untreated subjects not diagnosed with diabetes. The maximum AUC occurred at an HbA1c of 5.8%, but the differences in AUC from 5.5% to 7.0% were within the SEs of each other, indicating no obvious preferred HbA1c threshold.

Table S3 shows the ORs and 95% CIs for an elevated UACR of 30 mg/g or higher versus HbA1c category by NHANES examination cycle (7 to 10 inclusive).

4 | DISCUSSION

The NHANES dataset has been used to investigate the association of UACR with a number of pathologies including cardiovascular mortality¹⁷ and obstructive lung function,¹⁸ but this is the first study to examine the relationship of UACR with HbA1c. The current study shows that the percentage of elevated UACR is only significantly higher in those subjects with an HbA1c of 7.0% or higher compared with those subjects with HbA1c levels of less than 5.0%. There is no apparent linear trend for a greater prevalence of high UACR across HbA1c categories after excluding the 7.0% or higher category. The exception to this observation might be for those who are of Hispanic or Asian ethnicity whose groups had non-significant trends that might have become significant had the sample sizes of these groups been larger in the higher HbA1c categories. The OR estimates for these

FIGURE 2 Odds ratios (ORs) and 95% confidence intervals for the probability of urine albumin-to-creatinine ratio ≥ 30 mg/g according to HbA1c (%) categories versus the $<5\%$ HbA1c referent category for each race/ethnicity; N = 19 400, NHANES 2011-2018. Subjects selecting the other race category are not shown (N = 758). ORs were adjusted for age, gender, race, systolic blood pressure and current smoking status. Rx, treatment

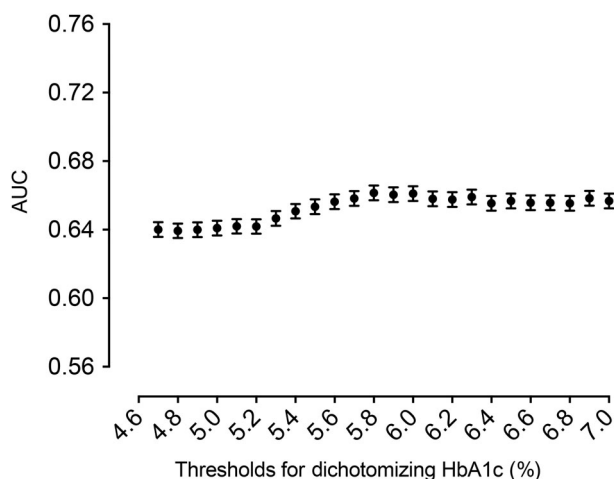
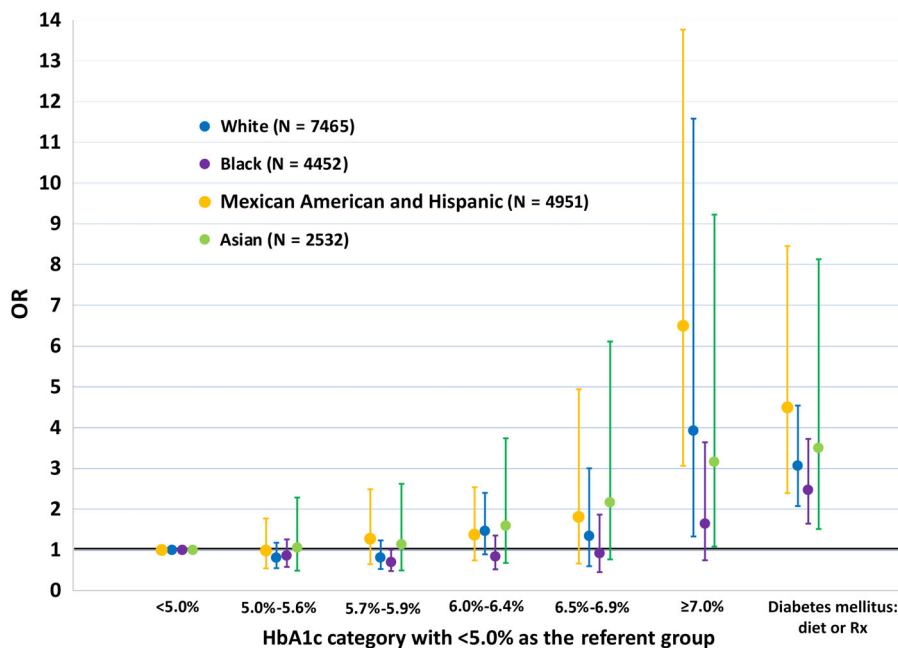


FIGURE 3 The area under the receiver operator curve (AUC) from logistic regression for each dichotomous HbA1c threshold from 4.7% to 7.0%; NHANES 2011-2018. Covariates included age, gender, race, systolic blood pressure and current smoking status

racial/ethnic groups were suggestive (1.4-2.2) for both the 6.0%-6.4% and 6.5%-6.9% HbA1c categories. Ethnic differences in nitric oxide capacity and UACR have been noted, which may in part account for these differences.¹⁹ These data agree with those for retinopathy, where the African American population had a notably higher prevalence of retinopathy at every level of HbA1c.¹⁴

A threshold analysis also does not show a specific HbA1c threshold for elevated UACR to predict a diagnostic HbA1c value for diabetes, in accord with a recent meta-analysis,¹⁴ even though there was an apparent linear progressive trend of increasing prevalence of elevated UACR as HbA1c increased in the population. The UACR OR showed a progressive increase up to an HbA1c of 7% and became significantly

greater than 1.0 at an HbA1c greater than 5.6%. The maximized best threshold of 5.8% for HbA1c determined from the AUC for the entire population was not very predictive of UACR because of the low sensitivity, as shown in the receiver operator curve. This range of possible cut-offs (5.7%-5.8%) is the cut-off above which patients have prediabetes, and others have suggested that the UACR is predictive of prediabetes²⁰; however, these albuminuria data do not help in resolving whether a diagnostic threshold for defining 'prediabetes' should be 5.7% (as suggested by the ADA) or 6.1% (as recommended in the UK).

Prediabetes has been shown to be modestly associated with an increase in chronic kidney disease and this suggests that aggressive management of prediabetes with chronic kidney disease may be warranted,²¹ particularly given the association of UACR with hypertension.²² However, even though higher SBP was strongly related to UACR in this study, adjustment for SBP only had a minor influence on the relationship between HbA1c and UACR.

Because the 6.0%-6.4% or the 6.5%-6.9% HbA1c categories versus HbA1c of less than 5% did not significantly increase the odds of having an elevated UACR, this suggests that the increasing ORs shown in Figure S1, as the HbA1c threshold is increased, were mainly driven by the high prevalence of raised UACR in those subjects not known to have diabetes who had an HbA1c of 7.0% or higher. As the HbA1c threshold was moved to lower levels, the percentage of subjects with a high UACR that were added to the high HbA1c group decreased, reducing the OR. The significant ORs only at higher HbA1c are in accord with a meta-analysis that suggested there was an increase in nephropathy defined by the UACR above an HbA1c of 6.5%,¹⁴ although only four studies were available for meta-analysis.¹⁴ From the category analysis of NHANES, non-significant ORs were similar for elevated UACRs for the 6.0%-6.4% and 6.5%-6.9% HbA1c categories versus the less than 5.0% HbA1c category (ORs of 1.4 and 1.3), and were similar to the meta-analysis non-significant prevalence

ratio of 1.35 (9.6%/7.1%)¹⁴ for HbA1c of 6.0%-6.4% versus less than 6.0%. These results suggest that some nephropathy is beginning to appear at the prediabetic HbA1c levels and may predict progression to diabetes,²⁰ but the prevalence is not yet significantly higher than at HbA1c levels of less than 5%.

An HbA1c level of 6.5% (48 mmol/mol) as the threshold for T2D diagnosis was recommended by the IEC based on the probability that individuals with HbA1c levels of 6.5% or higher have a markedly increased risk of retinopathy relative to those whose HbA1c falls below that threshold.⁸ This retinopathy-defined HbA1c threshold of 6.5% is lower than the 7.0% category that shows an elevated UACR risk in this study. This suggests that the 6.5% threshold is appropriate, because it will catch risks for both retinopathy and UACR, and that retinopathy was the appropriate microvascular complication to use to define the diagnostic threshold. This is in accord with a study in type 1 diabetes that reported that the risk of retinopathy and nephropathy did not differ at HbA1c levels of less than 6.5%, whereas complications occurred at 7.0% and above.²³

The strengths of this study are the well-described NHANES population that has been extensively studied. The limitations of this study are the comparatively few subjects in this cross-sectional evaluation with elevated HbA1c, which resulted in widening of the SEs. A larger sample size would be needed to definitively determine if there are racial differences in the increased elevation of UACR, especially at the higher HbA1c percentages. Ideally, a cohort study would be a better design, but to date these have not been performed to answer this question, and indeed the definition of 6.5% as the threshold for diabetes diagnosis based on retinopathy used cross-sectional studies such as DETECT-2.²⁴ In addition, any seasonal variations in UACR have not been taken into account, although the importance of this is unclear.²⁵ A further limitation is that there was only a single determination of UACR, and it is recognized that patients who may only have transient microalbuminuria would not display this in a repeated sample. In addition, the database is unable to exclude those patients with microalbuminuria and a low HbA1c because of kidney disease other than diabetic nephropathy. As NHANES is a cross-sectional probability sample of the US non-institutionalized population, the results may not be generalizable to other ethnic or global populations.

In conclusion, these data show that a clinically useful diagnostic threshold of less than 6.5% for HbA1c for elevated UACR risk was not identified, with a significantly increased risk beginning at an HbA1c of 7.0% or higher, and that using the retinopathy-derived HbA1c threshold of 6.5% also captures the risk for diabetic nephropathy in NHANES.

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CONFLICT OF INTEREST

None of the authors have any conflict of interest to declare.

AUTHOR CONTRIBUTIONS

SLA: conceptualization, data interpretation, manuscript writing and editing. AEB: manuscript writing and editing. SCH: statistical analysis,

data interpretation, manuscript writing and editing. ESK: conceptualization, data interpretation, manuscript writing and editing. SCH is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All the authors gave their consent for publication. SCH and ESK are joint senior authors.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14449>.

DATA AVAILABILITY STATEMENT

All the data for this study is publicly available.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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