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Association between body fat variation rate and risk of diabetic nephropathy - a posthoc analysis based on ACCORD database

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Abstract

Background Weight control has consistently been regarded as a significant preventive measure against diabetic nephropathy. however, the potential impact of substantial fluctuations in body fat during this process on the risk of diabetic nephropathy remains uncertain. This study aimed to investigate the association between body fat variation rate and diabetic nephropathy incident in American patients with type 2 diabetes.

Methods The study used data from the Action to Control Cardiovascular Risk in diabetes (ACCORD) trial to calculate body fat variation rates over two years and divided participants into Low and High groups. The hazard ratio and 95% confidence interval were estimated using a Cox proportional hazards model, and confounding variables were addressed using propensity score matching.

Results Four thousand six hundred nine participants with type 2 diabetes were studied, with 1,511 cases of diabetic nephropathy observed over 5 years. High body fat variation rate was linked to a higher risk of diabetic nephropathy compared to low body fat variation rate (HR 1.13, 95% CI 1.01–1.26). Statistically significant interaction was observed between body fat variation rate and BMI (P interaction = 0.008), and high level of body fat variation rate was only associated with increased risk of diabetic nephropathy in participants with BMI > 30 (HR 1.34 and 95% CI 1.08–1.66).

Conclusions Among participants with Type 2 Diabetes Mellitus, body fat variation rate was associated with increased risk of diabetic nephropathy. Furthermore, the association was modified by BMI, and positive association was demonstrated in obese but not non-obese individuals. Consequently, for obese patients with diabetes, a more gradual weight loss strategy is recommended to prevent drastic fluctuations in body fat.

Trial registration Clinical Trials. gov, no. NCT000000620 (Registration Date 199909).

Keywords Body fat variation rate, Diabetic nephropathy, Type 2 Diabetes, Body composition, Obesity

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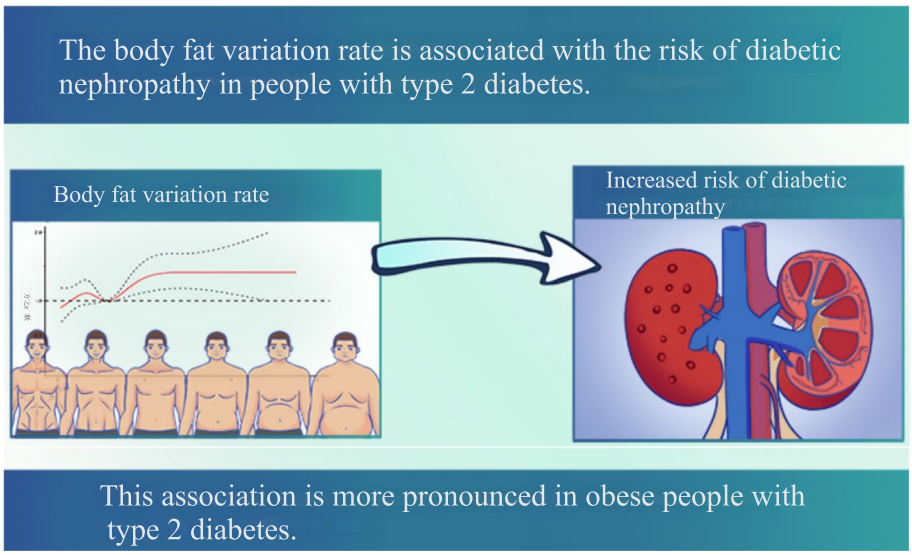
Graphical Abstract



Backgound

In recent times, diabetes has been considered as a global public health concern. According to the WHO, the predicted number of individuals with diabetes is anticipated to reach 592 million by 2035 [1]. Nevertheless, numerous studies indicate that the challenge posed by diabetes extends beyond merely managing blood sugar levels to meet established standards. Instead, it encompasses a range of microvascular complications associated with diabetes, notably including diabetes nephropathy (DN), diabetes retinopathy (DR), and diabetes peripheral neuropathy (DPN). Of the various complications associated with diabetes, DN has been found to have the highest incidence rates and poorest prognoses. A comprehensive analysis of diabetes cohort studies conducted in European and American countries revealed that between 20% and 40% of diabetes patients are at risk of developing DN [2, 3].

DN is classified as a microvascular complication characterized by a gradual decline in proteinuria and renal function. Various significant risk factors, such as hyperglycemia, hypertension, dyslipidemia, and obesity, contribute to its pathogenesis [4]. Of these factors, obesity is particularly noteworthy as a prominent and influential risk factor. This can be attributed to the increased challenges faced by obese individuals in achieving optimal regulation of blood pressure and blood sugar compared to non-obese individuals. As a consequence, individuals who are obese are at a heightened risk for developing DN due to the combined effects of suboptimal control of blood pressure and blood glucose levels [5]. Multiple research studies have indicated that the excessive deposition of adipose tissue is associated with an augmented autoinflammatory response, resulting in exacerbated microvascular impairment across different physiological systems. Consequently, obesity significantly contributes to the progression and onset of DN in individuals afflicted with type 2 diabetes mellitus (T2DM) [6]. Notably, a reduction in weight of 5–15% or more in obese individuals has been shown to significantly improve glycemic control in patients with T2DM and reduce the risk of DN [7–9]. Therefore, weight reduction through pharmaceutical interventions, dietary adjustments, or health education has become a vital approach to preventing or slowing the progression of DN. However, current research on obesity, weight loss, and DN primarily focuses on the relationship between obesity, weight loss, and DN without considering other potential factors. Furthermore, limited research exists regarding the potential impact of fluctuations in body composition, resulting from weight loss or changes in BFR, on the development of DN. The pursuit of weight loss or the maintenance of a stable weight can lead to significant changes in body composition. It is necessary to establish a suitable physical measurement index to assess whether these fluctuations may influence the onset and progression of DN. Consequently, a considerable number of researchers are interested in exploring the relationship between changes in obesity and DN by examining various physical indicators such as weight, BMI, waist circumference (WC),

waist height ratio (WHtR), and body fat rate (BFR) [10, 11]. Previous studies have shown a negative association between lean body mass and the likelihood of developing DN, while fat distribution has been found to be positively associated with DN specifically in male subjects [12]. Additionally, previous research has investigated the association between BMI and WC with the development of DN. The results of the study revealed a notable link between increased BMI variability and an increased likelihood of DN events, while WC did not show statistical significance [13]. However, despite the various methods of assessing body composition, some studies suggest that BFR may be a more accurate indicator of body composition [5]. There is a paucity of research examining the relationship between BFR and DN, possibly due to the complexity of its measurement indicators. Nonetheless, studies have demonstrated that BFR can be accurately predicted using a prediction equation based on BMI, age, sex, and other fundamental variables. Thus, this study employed a prediction equation to estimate American participant BFR and calculate the average real variability (ARV) between baseline and the second year in order to evaluate the relationship between BFVR and the risk of DN in individuals with T2DM.

Methods

Study design and participants

ACCORD is a randomized clinical trial that followed up on 10,251 T2DM patients from January 2001 to October 2005 to evaluate the health effects of enhanced blood glucose, lipid, and BP control on standard controls. The research design and main results have been published [14–17]. It involves dividing the population into three groups through analytic factor analysis following the principle of random assignment and ensuring that each group is balanced, specifically: (2) blood glucose test (HbA1c < 42 mmol/mol(6.0%) vs. 53 mmol/mol (7.0%) < HbA1c < 63 mmol/mol (7.9%)); (2) Lipid test (fenofibrate vs. placebo); (3) Blood pressure test (systolic blood pressure < 120mmHg compared to systolic blood pressure < 140mmHg). All participants in the blood glucose test were recruited from 77 clinical centers in North America (i.e. the United States and Canada). The ethical approval for the ACCORD study is granted by the institutional review committees of each clinical center, and written informed consent is obtained from all recruited participants. (Trial registration: Clinical Trials. gov, no. NCT000000620). In this posthoc study, we excluded subjects who lacked anthropometric indicators, age, gender, and other data at baseline, first year, and second year, as well as those who had previously defined ACCORD nephropathy events at baseline, first year, and second year. We also excluded patients with underweight (BMI < 18.5 kg/m^2) and overweight (BMI > 45 kg/m^2) measured at baseline.

Data collection and outcomes

The principal variables examined in our study are BFVR. Data on BFR were collected from all participants at three distinct time points: baseline, one year post-enrollment, and two years post-enrollment.Data pertaining to all covariates were obtained specifically from the second year of all participants. The BFR was determined using the Clinic Universidad Navarra Body Obesity Estimator prediction equation, which exhibited a strong association with the directly measured BFR ($r = 0.89$, $P < 0.000001$).The specific formula for the prediction equation is: BFR=-44.988+ (0.503 × Age)+ (10.689 × Gender)+ (3.172 × BMI −(0.026 × BMI ^{2})+ (0.181 × BMI × Gender −(0.02 × BMI × Age −(0.005 × BMI^2 × Gender)+ (0.00021 × BMI × Age) (Gender: 0 for males and 1 for females) [18]. Meanwhile, ARV is the average of the absolute differences between consecutive values and was calculated using the following formula:$ARV = \frac{1}{n-1} \sum_{k=1}^{N-1} \left|Value_{k+1} - Value_k\right|$, where n denotes the number of anthropo-metric measurements [19]. Using the median of the overall population's BFVR as the threshold, participants were grouped into two groups: high level of BFVR and low level of BFVR. The outcome of this study is the occurrence of DN, specifically defined as (1) doubling of serum creatinine or reduction of estimated glomerular filtration rate (eGFR)>20mL/min/1.73m2; (2) Urinary albumin/creatinine ratio (uacr) ≥ 300 mg/g; (3) Renal failure or ESRD (dialysis) or serum creatinine (SCr)>3.3 mg/dL without acute reversible cause. Participants who have experienced any of the events above are considered to have experienced DN.

Statistical analysis

The baseline characteristics of participants were summarized by presenting the frequency and percentage of categorical variables, along with the mean and standard deviation of continuous variables. Chi-square analysis was used to test the differences in categorical variables between groups, while t-tests or Wilcoxon tests were used for continuous variables. Kaplan Meier method was used to analyze the survival curve of DN incidence categorized by levels of BFVR. Cox proportional risk regression model was used to estimate the association between BFVR and DN, shown as hazard ratio (HR) with 95% confidence interval (CI). Three different models were calculated: model 1 was adjusted for age, sex, race, and BMI; model 2 was further adjusted for vitamin use (yes or no), smoking (yes or no), and alcohol consumption (yes or no); model 3 was further adjusted for glycosylated

hemoglobin, diastolic blood pressure, systolic blood pressure, low-density lipoprotein, high-density lipoprotein, very low-density lipoprotein, triglyceride levels, history of cardiovascular stroke (yes or no), and use of antihypertensive drugs (yes or no). Additionally, BFVR was treated as a continuous variable, and the corresponding HR and 95% CI of per 1-SD of BFVR and risk of DN were calculated. And covariates adjusted in models 1–3 was also adjusted here. Restricted cubic spline analyses were used to estimate the exposure-dose association between BFVR and DN in patients with T2DM.

Although ACCORD was a randomized controlled trial study, the baseline characteristics were not fully comparable when participants were grouped according to the level of BFVR. We used propensity score matching (PSM) with 1:1 nearest neighbor matching to balance the covariates between the two groups. The HRs and corresponding 95% CIs calculated above were re-estimated after PSM to alleviate the potential impact of some confounders.

Compared with nonobese people, obese people are more likely to have significant changes in BFR due to weight control, so this study further explores whether there are differences in the relationship between BFVR and DN in people with different BMI.

Subsequently, we proceeded to analyze the association between BFVR and the occurence risk of DN in individuals classified as obese (BMI $\geqq$ 30.0 kg/m^2) and non-obese (BMI < 30.0 kg/m^2), while also assessing the interaction between BFVR and BMI [20, 21].

All statistical analyses were conducted using a bilateral approach, and p value below 0.05 was considered statistically significant. All analyses were conducted using R Studio (version: 4.2.1) and Microsoft Excel.

Results

Classification of baseline features based on BFVR

Table 1 displays the baseline characteristics of 4,609 individuals diagnosed with T2DM who were included in the study.The participants were stratified into two groups, categorized as low level and high level, based on the median value of BFVR. Compared to low-level, the high-level group exhibited a higher likelihood of being

Table 1 Baseline characters of the unmatched and the matched

	Unmatched			**Matched**		
	Low	High		Low	High	
	n = 2305	*n* = 2304	*P* value	*n* = 1921	*n* = 1921	SMD
Age	65.5 (6.7)	64.4 (6.5)	< 0.0001	65.4 (6.6)	64.6 (6.6)	0.1179
Male	1425.00 (61.82)	1401.00 (60.81)	0.4984	1191.00(62.00)	1170.00(60.91)	0.0225
Years of Diabetes	10.73 (7.552)	10.58 (7.636)	0.5108	10.79 (7.57)	10.63 (7.56)	0.0214
Smoke	1230.00 (54.55)	1298.00 (58.13)	0.0169	851.00 (44.30)	792.00 (41.23)	0.0621
Alcohol	613.00 (26.59)	568.00 (24.65)	0. 14	511.00 (26.60)	484.00 (25.20)	0.0321
SBP	128.88 (15.90)	128.57 (16.57)	0.5223	128.80(15.69)	128.61(16.61)	0.0116
DBP	69.92.00(9.92)	69.73.00(10.15)	0.5226	69.81 (9.94)	69.57(10.14)	0.0236
CVD History	684.00 (29.67)	769.00 (33.38)	0.0075	586.00 (30.50)	650.00 (33.84)	0.0714
White Race Class	1496.00 (64.90)	1431.00 (62.11)	0.0525	1267.00 (65.96)	1219.00 (63.46)	0.0523
Trig	171.14 (119.09)	166.00(128.40)	0.1591	170.49(117.39)	165.39(119.61)	0.043
LDL	95.65 (32.49)	96.05 (35.22)	0.6865	95.88 (32.63)	96.04 (35.48)	0.0046
HDL	43.57 (11.65)	43.94 (13.14)	0.318	43.65 (11.46)	44.28 (13.38)	0.0512
ACEI	1209.00 (52.75)	1257 0.00(55.16)	0.109	1051.00 (54.71)	1077.00 (56.06)	0.0272
Waist	105.90(13.80)	107.51 (13.77)	0.0001	106.38(13.76)	107.49(13.72)	0.0802
Vitamin	1017.00 (44.84)	921.00 (40.90)	0.0081	891.00 (46.38)	812.00 (42.27)	0.0829
Early Decline in Kidney Function	1625.00(70.50)	1646.00 (71.44)	0.5015	1344.00 (69.96)	1368.00 (71.21)	0.0274
Early Diabetes	183.00 (7.94)	218.00 (9.46)	0.0748	159.00 (8.28)	174 0.00(9.06)	0.0278
A2RB	569.00 (24.83)	531.00 (23.30)	0.2412	474.00 (24.67)	445.00 (23.17)	0.0354
VLDL	33.36 (21.35)	32.42 (22.39)	0.1439	33.34 (21.38)	32.35 (20.99)	0.0469
HR	70.45 (11.43)	70.11 (11.38)	0.3225	70.30 (11.42)	69.75 (11.29)	0.049
BMI	31.99 (5.42)	32.61 (5.26)	0.0001	32.14 (5.39)	32.64 (5.24)	0.0942
Hba1c	7.16 (0.97)	7.02 (1.07)	< 0.0001	7.13 (0.95)	7.03 (1.06)	0.0985

Values are presented as median(interquartile range)or number(%).The dichotomous ranges were low(< 1.10745) and high(> 1.10745).P value for the test of the difference were obtained by using the x2 test (categorical variables), ANOVA (continuous variables), or Kruskal-Wallis test (nonparametric comparisons).SMD, Standard difference

younger, smokers, female, non-white, taking ACEI drugs, not taking ARB drugs, having a longer duration of diabetes, being abstainers, high HDL and BMI values, and low DBP and SBP values, as well as early diabetes and impaired renal function. After conducting PSM, the total population decreased to 3,842 individuals, with 1,921 individuals in each group. There was no statistically significant disparity in baseline covariates between the two groups, rendering them comparable both before and after matching.

The relationship between BFVR and DN in the general population

During the 5-year median follow-up period, a total of 1,511 cases of DN events were observed, with 784 DN cases occurring in the high level group and 727 DN cases in the low level group. The survival curve of DN incidence rates based on BFVR grouping is presented in Fig. 1. Table 2 demonstrates that compared to the low level group of BFVR, the high level group is associated with an increased risk of DN in model 3 (HR 1.13 and 95% CI 1.01–1.26). Furthermore, when BFVR is treated as a continuous variable, each 1-SD increase in BFVR is also linked to a higher risk of DN in model 3 (HR 1.12 and 95% CI 1.05–1.19). Simultaneously, in the subsequent multivariate adjusted restricted cubic spline analysis, a discernible pattern emerged within a specific range of BFVR, indicating a progressive increase followed by stabilization in the curve changes. This trend suggests a potential association between the HR of DN and the elevation of BFVR (Fig. 2). Finally, we repeated the above design in the matched population, and the results showed no significant changes compared to the above results.

Association between BFVR and DN in a subgroup analysis

In subgroup analysis, the relationship between BFVR and DN Analysis of different obesity subgroups showed that there was a statistically significant interaction between BFVR and BMI ($P_{interaction}$=0.008). During this 5-year median follow-up, there were 2,982 individuals in the obese group with 1,017 DN events, and 1,627 individuals in the non obese group with 494 DN events. In the obesity group, compared with the low level BFVR group again, the high level BFVR group is still related to the increased risk of DN in model 3 (HR 1.25 and 95% CI 1.09–1.43). And as a continuous variable, the increase of BFVR per 1-SD is also related to the risk of DN in model 3 (HR 1.15 and 95% CI 1.07–1.23). Again, in the restricted cubic spline analysis, the curve changes showed a trend of first increasing and then decreasing, suggesting that the HR of DN in obese people is still related to the increase of BFVR (Fig. 2). However, in the non obese group, whether the high level BFVR group is compared with the low level BFVR group, or as a continuous variable, there is no significant association with the risk of DN (Table 2) (Fig. 2). Additionally, we replicated

Table 2 Outcome risk analysis of the overall, obese and non-obese participants

Unmatched overall population outcome risk analysis(4,609)				
	Model1	Model2	Model3	Matched Model3
Variable	HR(95% CI) *P* value	HR(95% CI) *P* value	HR(95% CI) *P* value	HR(95% CI) *P* value
LOW BFVR	Ref	Ref	Ref	Ref
HIGH BFVR	1.11(1.00- 1.23) 0.05	1.11(1.00- 1.23) 0.05	1.13(1.01–1.26) 0.04	1.11(0.99–1.23) 0.06
Per 1 SD	1.09(1.03–1.16) <0.01	1.10(1.04–1.16) <0.01	1.12(1.05–1.19) <0.001	1.11(1.05–1.18) <0.01
Unmatched obese population outcome risk analysis(2982)				
	Model1	Model2	Model3	Matched Model3
Variable	HR(95% CI) *P* value	HR(95% CI) *P* value	HR(95% CI) *P* value	HR(95% CI) *P* value
LOW BFVR	Ref	Ref	Ref	Ref
HIGH BFVR	1.20(1.06–1.35) <0.01	1.19(1.05–1.35) <0.01	1.25(1.09–1.43) <0.01	1.24(1.08–1.42) <0.01
Per 1 SD	1.13(1.05–1.20) <0.001	1.13(1.05–1.21) <0.001	1.15(1.07–1.23) <0.001	1.14(1.07–1.23) <0.001
Unmatched non-obese population outcome risk analysis(1627)				
	Model1	Model2	Model3	Matched Model3
Variable	HR(95% CI) *P* value	HR(95% CI) *P* value	HR(95% CI) *P* value	HR(95% CI) *P* value
LOW BFVR	Ref	Ref	Ref	Ref
HIGH BFVR	0.92(0.77–1.10) 0.36	0.93(0.78–1.12) 0.46	0.96(0.79–1.17) 0.67	0.96(0.79–1.17) 0.68
Per 1 SD	1.02(0.91–1.13) 0.79	1.02(0.91–1.14) 0.71	1.04(0.92–1.17) 0.53	1.04(0.92–1.17) 0.53

Model1:Adjusted for sex, age, raceclass, BMI

Model2:Adjusted for model1 covariables plus smoke, alcohol, vitamin

Model3:Adjusted for model2 covariables plus HDL, LDL, VLDL, SBP, DBP, TG, ARB, ACEI, HbA1c, waist, early decline in kidney function, CVD history, years of diabetes.We also used propensity score matching to adjust all covariates to control confounding

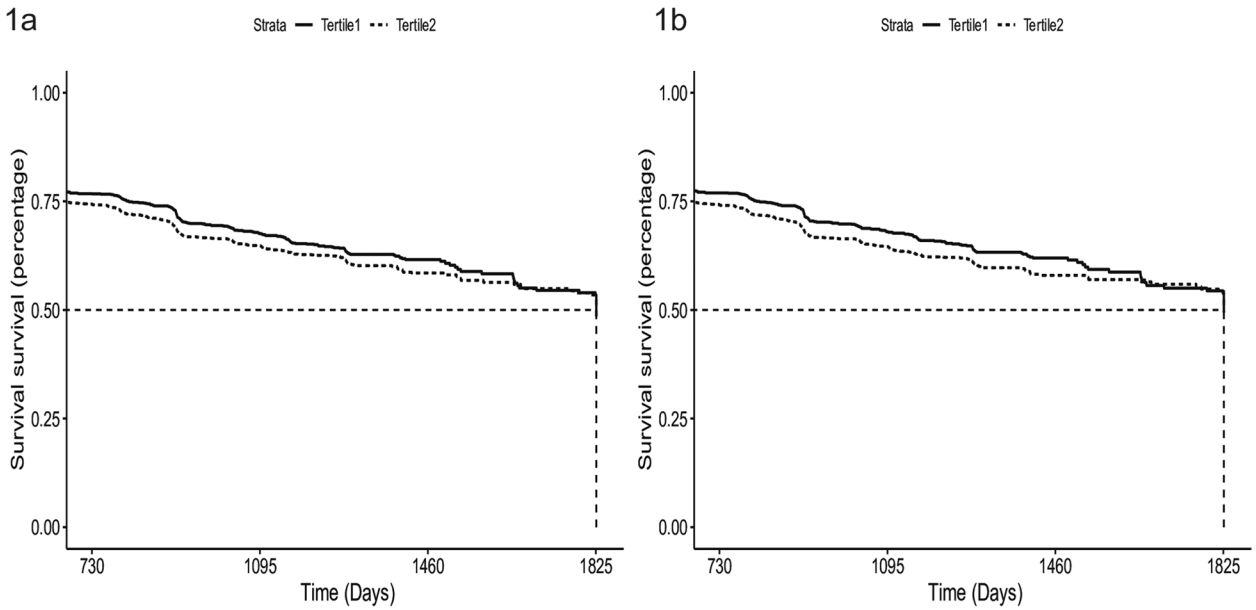


Fig. 1 Kaplan-Meier survival curve of the total population. Association of different levels of body fat variability with the cumulative probability of diabetic nephropathy (**1a**, **1b**). The highest curve is the population with lower body fat variation rate, and the second curve is the population with higher body fat varition rate. The results were analyzed again after matching and adjusting confounding factors for the population in the second picture

the design in the matched population and found similar results to the unmatched population.

Discussion

The findings of our study indicate a association between BFVR and an elevated risk of DN among individuals with T2DM. Upon stratification by BMI, this association was specifically evident in the obese subgroup (participants with BMI > 30.0), with a heightened risk compared to the overall study population. Thus, our research contributes epidemiological evidence supporting the link between fluctuations in body fat composition, as measured by BFVR, and the development of DN.

Appropriate weight loss, especially for obese patients, has many benefits, which is beyond doubt [22]. Previous research has consistently demonstrated the significant advantages of weight loss in preventing DN [7]. Additionally, studies have indicated that regardless of baseline renal function, patients experience notable improvements in renal function following weight loss, potentially even delaying progression to end-stage renal disease (ESRD) [23]. Furthermore, sustained long-term weight loss, defined as a reduction of at least 1%, has been associated with a decrease in the incidence of DN [24]. Recent scholarly research has proposed various perspectives suggesting that individuals with higher body weight or obesity generally exhibit lower morbidity and mortality rates from chronic diseases compared to those of normal weight. It has been posited that rapid or excessive weight loss may elevate the risk of developing DN. This argument highlights the potential emergence of an additional risk factor for DN in the context of rapid or excessive weight loss: fluctuations in body composition, which are often unavoidable during such weight loss [25]. Therefore, while weight loss or control may offer benefits for the prognosis of kidney disease, it is important to consider the impact of these fluctuations on the prognosis of kidney disease. Based on this understanding, studies have analyzed the association with microvascular complications of diabetes by taking the variability of WC and BMI as indicators to measure the fluctuation of body composition. The findings indicate a association between BMI variability and heightened risk of DN events [13]. Additionally, research has demonstrated that the impact of weight fluctuations on DN surpasses that of blood pressure and blood sugar control [26]. Despite the consensus among these studies regarding the significance of body composition changes in kidney disease, there remains considerable debate surrounding the use of metrics such as weight and BMI for evaluating body composition, with the persistence of the "obesity paradox" complicating such investigations. Thus, in the examination of the relationship between changes in body composition and the development of DN, this study carefully considered the selection of body measurement indicators. In the context of study indicating that BFR is

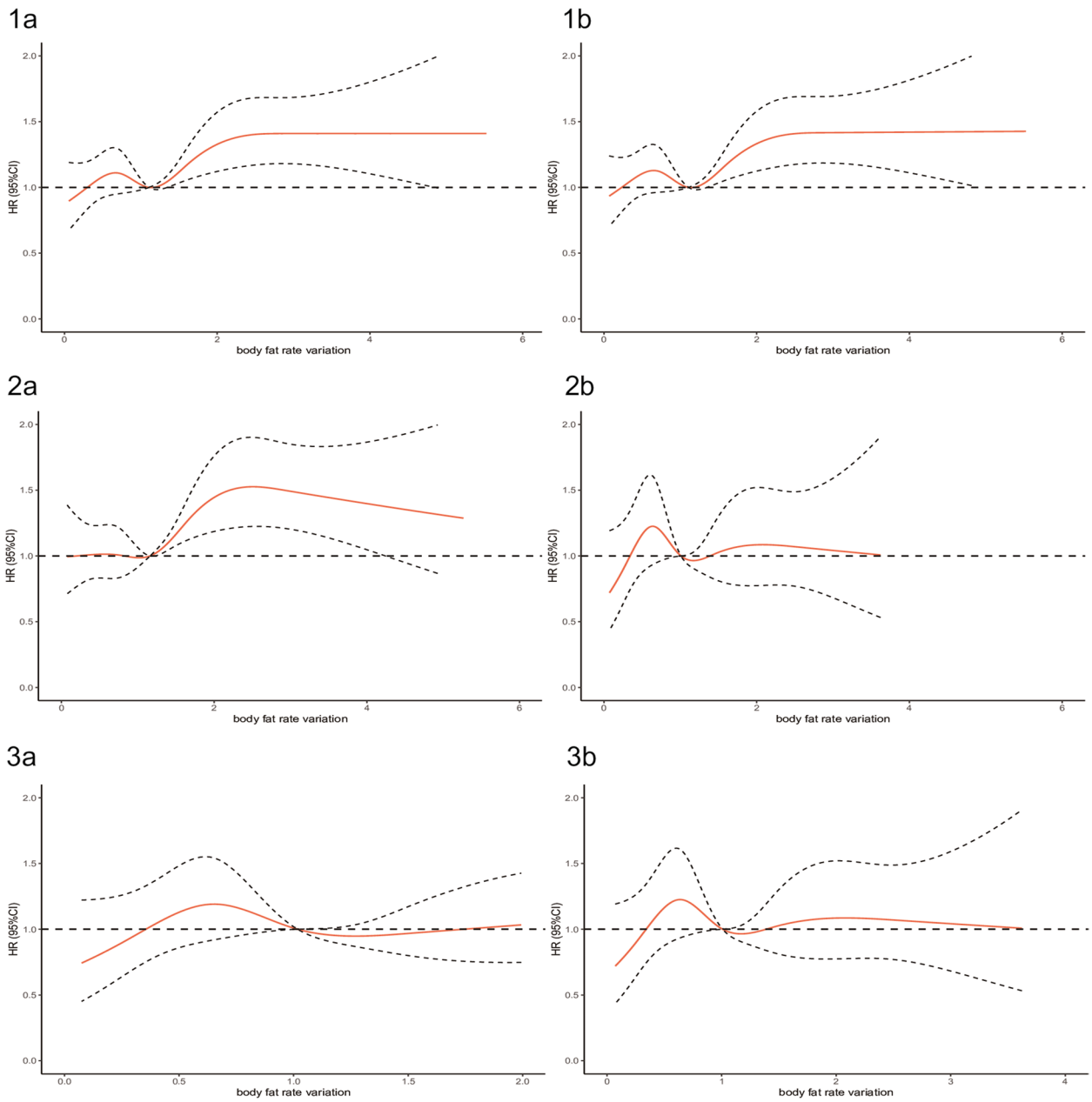


Fig. 2 Restricted cubic spline of body fat variability in different populations. Multivariate adjusted model risk ratio of body fat variability and diabetes nephropathy events in the overall population (**1a**, **1b**), obese (**2a**, **2b**) and non obese people (**3a**, **3b**). The curve represents the risk ratio of diabetes nephropathy adjusted based on the restricted cubic spline. The model was adjusted for participants' age, race, sex, BMI, glycated hemoglobin, blood glucose, blood pressure and lipids, duration of diabetes, alcohol consumption, smoking, history of hypertension, history of ACEI/ARB medication, history of cardiovascular disease, waist circumference, and early renal function decline during the second year. The solid red line represents the risk ratio, and the black line represents the 95% confidence interval for the association between the rate of variation in body fat and the overall outcome diabetic nephropathy. We also used propensity score matching to adjust all covariates for confounding in the above analysis

more suitable for the assessment of human obesity [27], BFVR was selected as an indicator to measure the fluctuation of body composition. The results obtained suggest that BFVR is related to the risk of DN, which is not only related to some discussions about weight. The research results of BMI variation rate and nephrotic event outcome are consistent [28–30], which also provide further evidence for the relationship between the indicators of

body composition fluctuation and the risk of DN. In contrast to prior research, this study conducted a more in-depth analysis of the relationship between the risk of DN in individuals with varying physical conditions (obese and non-obese). The findings revealed that the risk ratio of DN in obese individuals with high levels of BFVR was significantly higher compared to the general population. Furthermore, the study identified a positive association between an increase in BFVR per 1-standard deviation in obese individuals and an elevated risk of DN. Finally, further analysis using restricted cubic spline curves revealed that this association is only significant within a certain range of BFVR, indicating that the impact of this fluctuation on the body is restrictive. This also suggests the importance for individuals with obesity to monitor changes in BFR However, the precise range within which BFR with minimal impact on the obese population necessitates further investigation in more representative cohorts. Currently, the effect is notably significant when compared to the non-obese population. Therefore, it is imperative to control for fluctuations in BFR during weight management in obese individuals to mitigate the risk of DN complications.

However, the effect of BFVR on DN is unclear. Some studies suggest that increased fluctuations in body fat may lead to abnormal production of proinflammatory adipokines, potentially impacting microvascular diseases [31, 32]. Weight loss may disrupt the body's homeostasis, with excessive loss potentially causing harm. Finally, by combining BFVR growth every 1-SD with restricted cubic spline curve analysis, we discovered a self-limiting relationship between BFVR growth and outcome risk ratio within a specific range, this suggests that BFVR is linked to changes in body fat levels, with decreased body fat potentially reducing the risk of DN [33], increasing BFR may help offset this association.

One strength of our research lies in its substantial sample size and the availability of comprehensive clinical and biological data for all participants. Additionally, the minimal participant attrition in the database is another notable advantage. Nevertheless, this study is not without limitations. For instance, the ACCORD database does not specifically focus on weight loss; thus, despite our efforts to mitigate confounding variables through covariate adjustments and propensity score matching, the potential for residual confounding remains a concern.Simultaneously, the study only includes individuals with T2DM from North America, which may limit the generalizability of the findings.Furthermore, the study only shows a association between BFVR and the risk of DN, not a causal relationship. The formula used to calculate body fat percentage may not be the most accurate method. While the formula in question is based on the gold standard and demonstrates some level of predictive capability, it is evident that it influences the outcomes to a certain extent.

In summary, individuals with T2DM exhibit a association between BFVR and an increased risk of DN, with this association being influenced by BMI categorization. This relationship is particularly pronounced in individuals classified as obese, individuals with elevated BFVR levels are at a higher risk of developing DN compared to those with lower BFVR levels. Hence, it is imperative to not only monitor changes in body weight, BMI, and body fat levels, but also to consider the fluctuations in body fat.While additional research is required to determine the safety range of BFVR across diverse populations, it is incontrovertible that advising type 2 diabetes patients to consistently and reasonably reduce body fat and maintain stable weight can substantially mitigate the risk of DN.

Abbreviations

ACCORD	Action to Control Cardiovascular Risk in diabetes
T2DM	Type 2 Diabetes Mellitus
DN	Diabetes nephropathy
DR	Diabetes retinopathy
DPN	Diabetes peripheral neuropathy
WC	waist circumference
WHtR	waist height ratio
BFR	body fat rate
ARV	the average real variability
BFVR	body fat variability rate
SBP	systolic blood pressure
DBP	diastolic blood pressure
CVD	Cardiovascular disease
TG	Triglyceride
LDL	Low density lipoprotein
HDL	High-density lipoprotein
ACEI	angiotensin converting enzyme inhibitor
ARB	Angiotensin receptor blockers
VLDL	very low density lipoprotein
HR	Heart rate
BMI	Body mass index

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Not applicable.

Authors' contributions
S.L.,X.J.C.,C.C.L. contributed to the study concept and design; acquisition, analysis, and interpretation of the data; drafting and critical revision of the manuscript. L.L. contributed to the study concept and design; acquisition, analysis. X.Y.C., S.Y.L, M.G., contributed to the acquisition and interpretation of the data and critical revision of the manuscript. All authors gave final approval of the version to be published C.C.L. 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 accuracy of data analysis.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study has been conducted using the Action to Control Cardiovascular Risk in diabetes.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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