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Population and clinical strategies for the prevention of type 2 diabetes: What's new?

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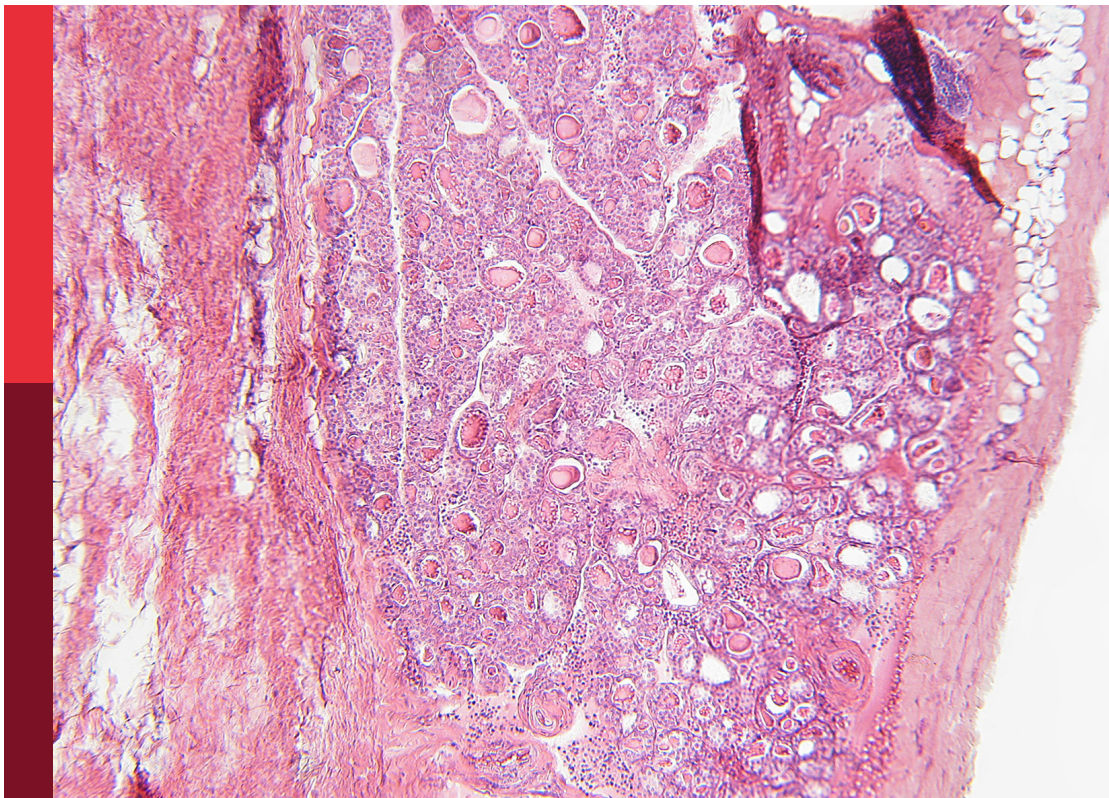
Published in
Frontiers in Endocrinology
Frontiers in Public Health



ISSN 1664-8714
ISBN 978-2-8325-4239-2
DOI 10.3389/978-2-8325-4239-2

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Population and clinical strategies for the prevention of type 2 diabetes: What's new?

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Citation

Schmidt, M. I., Herman, W., Bracco, P., Aschner, P., eds. (2024). *Population and clinical strategies for the prevention of type 2 diabetes: What's new?* Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-4239-2

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frontiers | Frontiers in Endocrinology

TYPE Editorial
PUBLISHED 19 December 2023
DOI 10.3389/fendo.2023.1348018

OPEN ACCESS

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RECEIVED 01 December 2023
ACCEPTED 06 December 2023
PUBLISHED 19 December 2023

CITATION
Schmidt MI, Aschner P, Bracco PA and Herman WH (2023) Editorial: Population and clinical strategies for the prevention of type 2 diabetes: what's new?.
Front. Endocrinol. 14:1348018.
doi: 10.3389/fendo.2023.1348018

Editorial: Population and clinical strategies for the prevention of type 2 diabetes: what's new?

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KEYWORDS

prediabetes, risk factors, screening, risk equations, intervention

Editorial on the Research Topic
Population and clinical strategies for the prevention of type 2 diabetes: what's new?

Diabetes is a growing clinical and public health problem. The International Diabetes Federation estimates that 537 million adults 20-79 years of age are living with diabetes worldwide and that by 2045, the number will increase to 783 million (1). This timely and important Research Topic of Frontiers in Endocrinology addresses new population and clinical strategies for the prevention of type 2 diabetes. Investigators from around the world describe risk factors for prediabetes and type 2 diabetes, screening for risk of type 2 diabetes, and interventions to prevent type 2 diabetes. Investigators describe skipping breakfast as an independent risk factor associated with prediabetes among Japanese adolescents (Miyamura et al.) and depression and post-traumatic stress disorder following the great east Japan earthquake, tsunami, and nuclear disaster as independent risk factors for new-onset diabetes mellitus in Japan (Hirai et al.). Other studies document the value of waist-corrected body mass index in predicting incident diabetes (Wang et al.) and impaired circadian patterns of blood pressure regulation (including non-dipping blood pressure levels) as a risk factor for new-onset diabetes in hypertensive patients with obstructive sleep apnea in China (Luo et al.). Other studies demonstrate that both low and high triglyceride to high-density lipoprotein cholesterol ratios are associated with risk for incident type 2 diabetes among Japanese men with normoglycemia (Song et al.) and that serum levels of neprilysin, a membrane bound zinc-dependent type II metallopeptidase responsible for the breakdown of glucagon and glucagon-like peptide 1, are independently associated with both prevalent diabetes and the future risk of diabetes in Chinese adults (Hu et al.).

With respect to screening for risk of type 2 diabetes, an international group of investigators demonstrated that it was feasible to rapidly implement FINDRISC, a non-

invasive screening tool for risk of type 2 diabetes based on age, body mass index, waist circumference, physical activity, daily intake of fruits and vegetables, history of hyperglycemia, history of antihypertensive drug treatment, and family history of type 2 diabetes, as part of a population-based screening campaign to detect people at risk for type 2 diabetes in 19 Latin America and Caribbean countries (Nieto-Martinez et al.). A second study based on a national survey of Brazilian adults demonstrated that most adults had good access to blood glucose testing and medical consultation (Santos et al.). Improvements in access were documented between 2013 and 2019 and in 2019, 77% reported having a glycemic test and 89% reported having access to a medical consultation in the past 2 years (Santos et al.). A third study, also from Brazil, demonstrated that risk equations that incorporate demographic, socioeconomic, lifestyle, clinical, and laboratory variables performed substantially better in predicting diabetes than fasting plasma glucose, 2-hour plasma glucose, and glycated hemoglobin used alone or in combination (Bracco et al.). Scores derived from multivariable equations that use continuously expressed clinical and laboratory variables detected more cases, identified fewer false positives, and consistently outperformed strategies based on categorical glycemic cut-offs (Bracco et al.).

With respect to interventions for diabetes prevention, a critical review of websites sponsored by business, government, and nonprofit organizations found that the top websites inadequately discussed dietary issues as causes, risk factors, and prevention strategies for type 2 diabetes (Crummett and Aslam). Websites are much more likely to discuss non-dietary lifestyle-associated risk factors such as physical activity and non-modifiable risk factors such as age (Crummett and Aslam). Based on the evidence that dietary interventions, with or without physical activity, can significantly decrease type 2 diabetes risk in both high-risk and general populations, the article concluded that diabetes websites should make a concerted effort to include more information about diet when discussing the causes, risk factors, and prevention of type 2 diabetes (Crummett and Aslam). Finally, in an article based on the report of the National Clinical Care Commission, a commission charged by the United States Congress to make recommendations to better leverage government policies and programs to more effectively prevent and control diabetes and its complications in the United States, the authors called for increased recognition of diabetes as a complex societal problem as well as a biomedical problem (Herman and Schillinger). They argued that the prevention and control of type 2 diabetes in the United States must begin with concrete population-level interventions to address social and environmental determinants of health including government policies and programs that address food and agriculture, education, housing, transportation, trade, commerce, and the environment (Herman and Schillinger).

Better definition of risk factors for type 2 diabetes, simpler and more efficient screening approaches to identify at-risk individuals, and both targeted and population level interventions are needed to prevent type 2 diabetes. We hope that this Research Topic of papers will provide you with insights about new opportunities and strategies to address the pandemic of type 2 diabetes.

Author contributions

MS: Writing – review & editing. PA: Writing – review & editing. PB: Writing – review & editing. WH: Writing – original draft.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Reference

1. International Diabetes Federation. *IDF Diabetes Atlas* (2021). Brussels, Belgium *10th edn*. Available at: https://www.diabetesatlas.org (Accessed November 20, 2023).

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 10 November 2022
DOI 10.3389/fendo.2022.1035017

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Clinical Diabetes, a section of the journal Frontiers in Endocrinology

RECEIVED 02 September 2022
ACCEPTED 27 October 2022
PUBLISHED 10 November 2022

CITATION
Lan B, Bai Y, Chang X and Zhang X (2022) Independent and joint effect of relative telomere length and type 2 diabetes on all-cause mortality in American adults. *Front. Endocrinol.* 13:1035017. doi: 10.3389/fendo.2022.1035017

Independent and joint effect of relative telomere length and type 2 diabetes on all-cause mortality in American adults

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Objective: The joint effect of leukocyte telomere length (LTL) and type 2 diabetes (T2D) on the risk of all-cause death has been sparsely explored. The study designed to examine the joint effect of T2D and LTL on the probability of death in American adults.

Methods: A cohort of 6862 adults with LTL measurements and with or without T2D from the NHANES 1999-2002 with follow-up information until 2015 was studied. Quantitative PCR was used to measure the length of telomeres relative to standard reference DNA (T/S ratio). Individuals were grouped into three tertiles according to the LTL levels, with the first tertile demonstrating the lowest one and used as the reference group. The effects of LTL and T2D status on death were evaluated using Kaplan–Meier curves along with log-rank test. Three Cox proportional hazards models with adjustment for various confounders were used to examine the links between TL and all-cause death possibility using adjusted hazard ratios (HRs).

Results: Adults in the sample averaged 45.54 years of age, with 49.51% being male. After a median follow-up period of 14.4 years, 1543 (22.5%) individuals died from all cause. The probability of all-cause mortality was higher among individuals with LTL in the highest tertile than individuals in the lowest tertile (aHR = 0.89; 95%CI: 0.77-1.03); however, the difference did not reach the level of statistical significance (P = 0.11). Conversely, the individuals with T2D had a higher probability of death than individuals without (aHR = 1.26; 95%CI: 1.06-1.50; P = 0.0092). When LTL and T2D status were investigated jointly, subjects in the highest TLT tertile and with T2D had the highest probability of mortality compared with their counterparts (aHR = 1.34; 95%CI: 1.07-1.68; P = 0.0101). However, there was no independent effect of low TLT on mortality as demonstrated among individuals with diabetes (aHR = 1.14; 95%CI: 0.95-1.38; P = 0.1662).

Conclusion: The joint effect of TLT and T2D was larger than the sum of the independent effects on the risk of all-cause death. Participants with high TLT and diabetes showed the highest possibility of death compared with other groups.

KEYWORDS

telomere length, diabetes, mortality, NHANES, database

Introduction

The worldwide prevalence of diabetes in adults has increased dramatically over recent decades, which has become as a significant cause of morbidity and mortality globally (1). Type 2 diabetes (T2D) is a chronic metabolic disorder related to multiple complications with a worldwide distribution, which characterized by insulin resistance and hyperglycemia and can affect multiple organ systems (2). Among the numerous chronic diseases, T2D is now one of the most recognized diseases globally and it is anticipated that by the year 2030 around 580 million individuals will suffer from it (3, 4).

The telomeres at the ends of chromosomes serve as protective structures for the ends of eukaryotic chromosomes (5). Telomere shortening is associated with older age as well as undesirable lifestyle factors such as smoking, overweight and alcohol abuse (6). There is emerging evidence that the length of leukocyte telomeres (LTL) can serve as a marker for organismal aging, as well as for well-established age-related diseases such as coronary heart disease, Alzheimer's disease, and diabetes (7–10). As T2D has been commonly considered as an adult age–related disease, it may be associated with LTL. However, the relationship between LTL and T2D is still not clear. Previous studies have detected telomere shortening in T2D, while others have revealed a negative co –relation of LTL and T2D (11, 12). Furthermore, the significance of LTL as a prognostic indicator for death in the general population is conflicting. Two previous cohort reports have revealed that LTL is a biomarker of mortality (13, 14), while other prospective studies have failed to demonstrate such association (15, 16). As for diabetes, two studies in European populations with relatively small sample size found that LTL was associated with all-cause death in type 1 diabetes, and LTL combined with clinicopathological characteristics can provide additional prognostic significance on death probability in T2D individuals (17, 18). According to a recent study, shorter LTL was associated with an elevated mortality rate among individuals with T2D in the Chinese population (19). Both T2D and LTL were related to aging, however, the effect of exposure to T2D with LTL on all-cause mortality in American adults has not been evaluated till now.

This study designed to explore whether LTL can, independently and jointly with T2D, influence the possibility of all-cause death using data from the NHANES. Understanding this association could contribute to prevent T2D and develop health promotion programs.

Materials and methods

Study populations

Information of individuals enrolled in the NHANES 1999–2002, a nationally representative survey sample of civilian noninstitutionalized US population was utilized. In brief, as an ongoing cross-sectional survey, the NHANES surveys using complex, multi-stage and probability sampling approaches to estimate the health and nutritional status of the civilians in US and to provide vital and health statistics for the nation. NHANES organizes the family face-to-face interviews, medical examination, laboratory examination, and further gathers the details about the demographics, lifestyles factors, dietary intake, health status and medical history.

A total of 21,004 individuals were recorded in the initial analysis. Individuals with missing records for telomere test were excluded (N = 13,177). We further ruled out 751 subjects without reporting diabetes status. Because NHANES recorded who were ≥85 years old as 85 years, subjects younger than 18 years and older than 85 years were excluded (N = 211). Finally, missing data regarding follow-up were excluded (N = 3), thus yielding the sample size to 6,862 eligible adults (Figure 1).

Measurements of LTL

LTL measures are available for two cycles of NHANES from 1999 to 2002. Blood samples containing their DNA were collected from all adults and stored at −80°C at the Centers for Disease Control and Prevention (CDC). For DNA analysis, qPCR assays were carried out at a laboratory in San Francisco, California to measure the telomere length relative to standard reference DNA, as described in detail elsewhere previously (20). LTL was determined and compared as telomere-to-single copy gene ratio (T/S ratio). According to NHANES, qPCR was carried

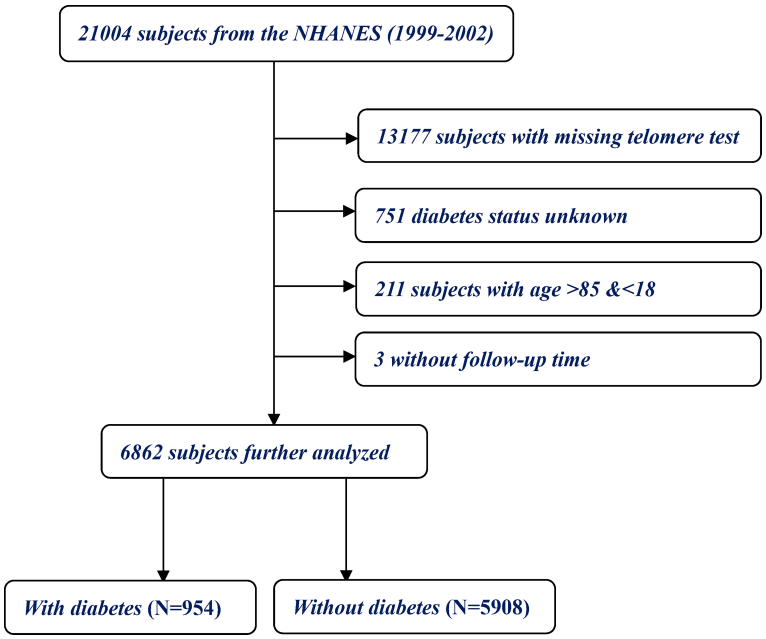

FIGURE 1
The detailed flow-chart of study population selection.

out three times on three different days, and the samples were assayed in duplicate wells to gain 6 data points. Full details regarding the LTL measurement are open and available and listed on the NHANES web at: https://wwwn.cdc.gov/Nchs/Nhanes/2001-2002/TELO_B.htm. The CDC Institutional Review Board provided human subject approval for the study.

Study variables

The NHANES physical examination in our study mainly involved measurement of waist circumference, height, weight, and body mass index (BMI), which was computed as weight in kg divided by height in m, squared. Information on age (years), sex (male, female), family poverty income ratio, race/ethnicity (Mexican American, non-Hispanic Black, non-Hispanic White, and others), education (less than high school, high school diploma, and more than high school), marital status (married, unmarried), smoking (current smoker, former smoker and never smoker), history of antidiabetic drug, and alcohol drinking was based on self-report during the questionnaire portion of the survey. For simplicity, there were two categories of marital status, namely, unmarried (widowed/divorced/separated/never married) and married (living as married). Alcohol drinking was defined as an individual who had alcohol abuse at least 12 times per year. Furthermore, individuals' history of cardiovascular disease (CVD), cancer, asthma, and hypertension was obtained. Metabolic Syndrome (MetS) was defined as individuals with the evidence of three or more of five components (abdominal obesity, elevated triglycerides, blood pressure, fasting blood glucose, and reduced high-density lipoprotein cholesterol) (21). Participants were considered to have a history of CVD if they had been told that they had congestive heart failure, angina, stroke, coronary heart disease, or heart attack. According to the American Diabetes Association (22), the diagnostic criteria for T2D are made if any of the following conditions presented (1): doctor told you have diabetes (2); glycohemoglobin HbA1c (%) > 6.5; (3) fasting glucose ≥ 7mol/L; (4) random blood glucose ≥ 11.1 mmol/L; (5) Oral antidiabetic medication. Using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, we estimated the glomerular filtration rate (eGFR) (23). In regard to general biochemistry tests, creatinine (mg/dl), serum albumin (g/dl), C-reactive protein (mg/dl), high-density lipoprotein (HDL) cholesterol (mg/dl), uric acid (mg/dl), and total cholesterol (mg/dl) were enrolled. Details regarding the full procedures of laboratory tests can be obtained on the official website at https://wwwn.cdc.gov/nchs/nhanes.

Mortality follow-up data

Survival status data was downloaded from the National Death Index (NDI). The NHANES data was merged with the NDI using a unique study identifier. The detailed mortality records are available online at https://www.cdc.gov/nchs/

datalinkage/mortality-public.htm. Adult individuals were followed for mortality through December 31, 2015 to ascertain survival status. The primary endpoint event was all-cause death. The cause of death in the present study was based on ICD-10 system codes.

Statistical analysis

According to the NHANES recommendation and guidelines, an appropriate sampling weight for the variable of interest that was collected on the smallest number of respondents was calculated and accounted for complex multistage survey design strategies in the analysis. In the survey, continuous variables were expressed as a survey-weighted mean with 95% confidence intervals (CI), whereas categorical variables were expressed as survey-weighted percentages with 95% confidence intervals (CI). The LTL levels were divided into three tertiles, with the first tertile representing the lowest level and being considered the reference group. In comparison with those in tertile 1, the hazard ratios (HRs) and 95% CIs for subjects in tertile 2 and 3 were computed. A potential confounder was selected if it altered LTL estimates by more than 10% or was notably associated with mortality (24). The effects of LTL and T2D status on death were evaluated using Kaplan–Meier curves along with log-rank test. Three Cox proportional hazards models were utilized with adjustment for potential confounders. As for model 1, no confounding factors were adjusted. A model 2 had adjustment for age, sex, and smoking. Model 3 was further adjusted for cancer, hypertension, CVD, MetS, eGFR, albumin, and antidiabetic drug. It was considered statistically significant if the *P*-value was less than 0.05. A variety of analyses were performed with Empower software (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA, USA) and R version 3.6.3 (http://www.Rproject.org, The R Foundation).

Results

A description of a person's characteristics

In total, 6862 adults participated in the study, which included 954 individuals with T2D and 5908 without. An overview of the demographic baseline characteristics of the included individuals can be found in Table 1. People on average were 45.5 years old, with 49.5% being males. The weighted mean (95% confidence interval) of LTL concentration was 1.06 (1.03, 1.09).

Compared with individuals with LTL in the lower tertile (T1–T2), individuals in the highest tertile (T3) had a lower mean age, BMI, waist circumference, C-reactive protein, creatinine, total cholesterol, high school diploma, married status, history of cancer, hypertension, CVD, and MetS at baseline, and had a higher albumin, eGFR, and now smoking. Compared with individuals without T2D, individuals with T2D had higher mean age, BMI, waist circumference, C-reactive protein, creatinine, total cholesterol, uric acid, and more male, Mexican American, non-Hispanic Black, former smoking, history of cancer, hypertension, CVD, and MetS at baseline. Participants with T2D had lower family poverty income ratio, albumin, HDL-cholesterol, eGFR, alcohol drinking, never smoking, and now smoking.

Association between LTL, T2D and mortality

During a mean of 160 months of follow-up, 1543 deaths from all causes were identified. In Table 2, Cox regression analysis was adopted to assess the individual effect of LTL and T2D on all-cause risk. When LTL was used as continuous variable, LTL was associated with reduced risk of death in the crude model (HR = 0.10, 95%CI= 0.08-0.12; $P < 0.0001$), and model I (aHR = 0.78, 95%CI = 0.62-0.99; $P = 0.0389$). However, in the full adjusted model, LTL was not associated with a lower risk of death (aHR = 0.82, 95%CI= 0.65-0.1.04; $P = 0.0944$). The results remained when LTL was used as categorical variable. LTL in the higher tertiles (T2, T3) was not associated with decreased risk of death in the full adjusted model (aHR = 0.95, 95%CI = 0.85-1.07; $P = 0.4207$; aHR = 0.89, 95%CI = 0.77-1.03; $P = 0.1100$, respectively). When individuals without T2D were used as reference, it was found a significant association between LTL and all-cause mortality in the crude model (HR = 2.95, 95%CI= 2.64-3.29; $P < 0.0001$), model I (aHR = 1.57, 95%CI = 1.40-1.75; $P < 0.0001$), and the full adjusted model (aHR = 1.26, 95%CI = 1.06-1.50; $P = 0.0092$).

When LTL and T2D were investigated together, the Kaplan-Meyer curves demonstrated that the cumulative hazard of death notably differed among the four groups defined by LTL and T2D categories (comparing LTL in the T1-T2 and T3 among those individuals without T2D, the $P < 0.001$; comparing LTL in the T1-T2 and T3 among those individuals with T2D, the $P < 0.0001$; Figure 2). As presented in Figure 3, within each stratum of diabetes, there was a negative association between tertiles of LTL and risk of death in unadjusted model ($P_{\text{for trend}} < 0.001$). However, the all-cause death risk was higher among the individuals with T2D.

The Cox proportional hazards regression analyses in Table 3 revealed that the highest probability of all-cause death was in the group with highest LTL tertile and T2D, with an HR of 1.34 (95% CI = 1.07–1.68; $P = 0.0101$) after adjusting for age, smoking, cancer, sex, CVD, MetS, hypertension, eGFR, albumin, and antidiabetic drug. However, for individuals in lower LTL tertile (T1-T2), the all-cause mortality was comparable regardless of the T2D status (aHR = 1.14,

TABLE 1 Baseline characteristics of participants by telomere length tertiles and status of diabetes, weighted.

Characteristics	First to two tertiles (0.39-1.11)	Third tertiles (1.11-3.31)	P-value	Without diabetes	With diabetes	P-value
Age, years	49.46 (48.56,50.36)	38.92 (37.65,40.20)	<0.0001	44.26 (43.55,44.98)	57.80 (56.22,59.37)	<0.0001
Body mass index, kg/m^2	28.34 (28.03,28.65)	27.44 (27.05,27.83)	0.0002	27.57 (27.31,27.83)	32.31 (31.43,33.20)	<0.0001
Waist circumference (cm)	97.11 (96.31,97.91)	93.50 (92.48,94.51)	<0.0001	94.48 (93.82,95.14)	108.52 (106.47,110.58)	<0.0001
Family poverty income ratio	3.05 (2.90,3.21)	2.95 (2.79,3.12)	0.2175	3.06 (2.91,3.20)	2.62 (2.44,2.79)	<0.0001
Albumin (g/dl)	4.36 (4.34,4.38)	4.42 (4.38,4.45)	0.0014	4.40 (4.37,4.42)	4.25 (4.21,4.28)	<0.0001
C-reactive protein(mg/dl)	0.45 (0.42,0.48)	0.35 (0.31,0.38)	0.0001	0.39 (0.36,0.41)	0.66 (0.60,0.72)	<0.0001
Creatinine (mg/dl)	0.85 (0.83,0.87)	0.81 (0.80,0.83)	0.0205	0.83 (0.81,0.84)	0.92 (0.87,0.96)	0.0006
HDL-cholesterol (mg/dl)	50.77 (49.72,51.83)	51.37 (50.52,52.22)	0.3547	51.60 (50.75,52.45)	45.18 (44.05,46.30)	<0.0001
Total cholesterol (mg/dl)	205.71 (203.26,208.17)	197.67 (195.80,199.53)	<0.0001	202.16 (200.22,204.10)	208.08 (203.06,213.10)	0.0293
eGFR (CKD-EPI formula), ml/min per 1.73 m^2	90.32 (89.38,91.26)	100.24 (99.16,101.33)	<0.0001	95.03 (94.00,96.05)	84.25 (82.35,86.15)	<0.0001
Uric acid (mg/dl)	5.41 (5.35,5.47)	5.31 (5.22,5.39)	0.0682	5.34 (5.29,5.39)	5.65 (5.49,5.82)	0.0011
Sex (%)			0.5851			0.0016
Female	50.82 (49.02,52.62)	49.94 (47.93,51.95)		51.00 (49.89,52.10)	45.67 (42.53,48.84)	
Male	49.18 (47.38,50.98)	50.06 (48.05,52.07)		49.00 (47.90,50.11)	54.33 (51.16,57.47)	
Race (%)			0.0017			<0.0001
Mexican American	6.94 (5.05,9.46)	6.84 (5.11,9.11)		6.89 (5.36,8.83)	7.03 (4.79,10.20)	
Non-Hispanic Black	7.69 (5.82,10.10)	11.90 (9.31,15.09)		8.84 (6.98,11.13)	13.34 (10.20,17.27)	
Non-Hispanic White	75.89 (71.24,80.00)	68.26 (63.45,72.70)		73.90 (70.14,77.33)	64.86 (58.72,70.55)	
Others	9.48 (6.23,14.16)	13.00 (9.15,18.15)		10.37 (7.37,14.42)	14.77 (9.34,22.57)	
Education (%)			0.0004			<0.0001
Less Than High School	22.51 (20.25,24.93)	18.15 (16.35,20.11)		19.46 (17.61,21.46)	34.55 (30.22,39.16)	
High School Diploma	26.48 (24.15,28.94)	25.62 (22.96,28.47)		26.18 (24.00,28.49)	25.91 (22.02,30.23)	
More Than High School	51.02 (47.50,54.53)	56.23 (52.91,59.50)		54.35 (51.02,57.65)	39.54 (35.22,44.03)	
Marital status (%)			0.0001			0.6852
Unmarried*	32.35 (30.39,34.38)	39.26 (35.86,42.77)		34.74 (32.54,37.02)	35.96 (30.78,41.48)	
Married	67.65 (65.62,69.61)	60.74 (57.23,64.14)		65.26 (62.98,67.46)	64.04 (58.52,69.22)	
Alcohol drinking (%)			0.1254			<0.0001
No	28.11 (24.79,31.68)	24.95 (20.00,30.65)		25.66 (21.93,29.79)	39.24 (35.52,43.08)	
Yes	71.89 (68.32,75.21)	75.05 (69.35,80.00)		74.34 (70.21,78.07)	60.76 (56.92,64.48)	
Smoking (%)			<0.0001			<0.0001
Never	48.12 (45.48,50.77)	53.07 (48.95,57.14)		50.37 (47.71,53.03)	45.96 (41.04,50.96)	
Former	28.14 (25.77,30.65)	19.81 (17.71,22.08)		24.10 (22.32,25.98)	34.10 (30.20,38.23)	
Now	23.74 (21.53,26.10)	27.13 (23.83,30.69)		25.52 (23.53,27.63)	19.94 (16.88,23.40)	
Cancer (%)			<0.0001			<0.0001
No	90.74 (89.29,92.00)	95.48 (94.14,96.52)		93.05 (92.01,93.96)	87.21 (83.92,89.90)	
Yes	9.26 (8.00,10.71)	4.52 (3.48,5.86)		6.95 (6.04,7.99)	12.79 (10.10,16.08)	
Hypertension (%)			<0.0001			<0.0001
No	69.30 (66.70,71.77)	79.66 (77.16,81.96)		76.21 (74.02,78.26)	43.79 (39.38,48.29)	
Yes	30.70 (28.23,33.30)	20.34 (18.04,22.84)		23.79 (21.74,25.98)	56.21 (51.71,60.62)	
Asthma (%)			0.5392			0.935
No	88.32 (86.69,89.78)	88.97 (86.95,90.70)		88.55 (87.14,89.82)	88.70 (84.38,91.94)	
Yes	11.68 (10.22,13.31)	11.03 (9.30,13.05)		11.45 (10.18,12.86)	11.30 (8.06,15.62)	
CVD (%)			<0.0001			<0.0001
No	89.64 (88.42,90.74)	96.14 (94.78,97.16)		93.63 (92.75,94.42)	76.89 (72.14,81.04)	
Yes	10.36 (9.26,11.58)	3.86 (2.84,5.22)		6.37 (5.58,7.25)	23.11 (18.96,27.86)	

(Continued)

TABLE 1 Continued

Characteristics	First to two tertiles (0.39-1.11)	Third tertiles (1.11-3.31)	P-value	Without diabetes	With diabetes	P-value
MetS (%)			0.0005			<0.0001
No	89.96 (88.87,90.97)	93.22 (91.60,94.54)		94.52 (93.74,95.20)	59.01 (54.55,63.32)	
Yes	10.04 (9.03,11.13)	6.78 (5.46,8.40)		5.48 (4.80,6.26)	40.99 (36.68,45.45)	
Antidiabetic						<0.0001
No	93.64 (92.66,94.50)	96.17 (94.77,97.20)	0.0018	100.0(100.0, 100.0)	42.32 (37.66,47.11)	
Yes	6.36 (5.50,7.34)	3.83 (2.80,5.23)		0.0(0.0, 0.0)	57.68 (52.89,62.34)	

*Included divorced/never married/separated/widowed.

95% CI = 0.95–1.38; P = 0.1662). Nevertheless, in individuals without T2D, higher LTL tertile was associated with a decreased risk of all-cause death when compared with those individuals with lower LTL tertile (aHR = 0.86, 95% CI = 0.75–0.98; P = 0.0240).

Discussion

T2D is characterized by increased blood glucose values, while the LTL is used as a biological biomarker of cell ageing. Previous studies have demonstrated that shortened LTL was significantly associated with incident T2D (11, 25). Thus, this study designed to find the joint effect of T2D and LTL on the risk of mortality in American adults. In this prospective cohort study, the results indicate that regarding all-cause death the joint effect of T2D and elevated LTL is larger than the sum of their individual effects. These results demonstrate that controlling T2D may bring an additional risk reduction regarding all-cause death.

Telomere shortening is confirmed as a key molecular mechanism of vascular aging (26), and shorter telomere length has been related to age-related diseases including T2D (27). Telomere length shortens gradually during each cell division cycle, and is inversely associated with the total times of cell divisions (28). Previous studies have exhibited an association of mean LTL shortening in patients with T2D (29, 30). The study has contributed new insights to LTL and T2D. So far, the role of T2D and LTL on the risk of mortality has not been examined thoroughly.

In our study, we demonstrated a joint effect of T2D and LTL on the risk of mortality in American adults. The highest probability of all-cause death was noted in the group with highest LTL tertile and T2D. Furthermore, we also found that in individuals without T2D, higher LTL tertile was associated with a decreased risk of all-cause death when compared with those individuals with lower LTL tertile. A recent meta-analysis contained 6,991 individuals and 2,011 incident T2D events concluded that the combined relative risk for T2D incidence was 1.31 when comparing the lowest with the highest LTL at baseline (31). These findings support the view that telomere shortening is a pivotal hallmark of cellular senescence and organismal aging. Individuals with shorter LTL at baseline exhibit a higher probability of mortality during follow-up when compared to those with longer LTL in general population after adjusting for multiple traditional risk factors (19). However, not all studies supported a positive link between

TABLE 2 Individual effect of telomere length (T/S ratio) and diabetes on all-cause mortality.

Exposure	Non-adjusted	Adjust I	Adjust II
Telomere Length (T/S ratio)	0.10 (0.08, 0.12) <0.0001	0.78 (0.62, 0.99) 0.0389	0.82 (0.65, 1.04) 0.0944
Telomere Length (T/S ratio) tertiles			
Tertile 1	1 (Ref)	1 (Ref)	1 (Ref)
Tertile 2	0.51 (0.46, 0.58) <0.0001	0.91 (0.81, 1.02) 0.1172	0.95 (0.85, 1.07) 0.4207
Tertile 3	0.30 (0.26, 0.34) <0.0001	0.86 (0.75, 0.99) 0.0400	0.89 (0.77, 1.03) 0.1100
Diabetes			
No	1 (Ref)	1 (Ref)	1 (Ref)
Yes	2.95 (2.64, 3.29) <0.0001	1.57 (1.40, 1.75) <0.0001	1.26 (1.06, 1.50) 0.0092

Non-adjusted model adjust for: None.
Adjust I model adjust for: Age, sex, and smoking.
Adjust II model adjust for: Age, sex, smoking, cancer, hypertension, CVD, MetS, eGFR, albumin, and antidiabetic drug.

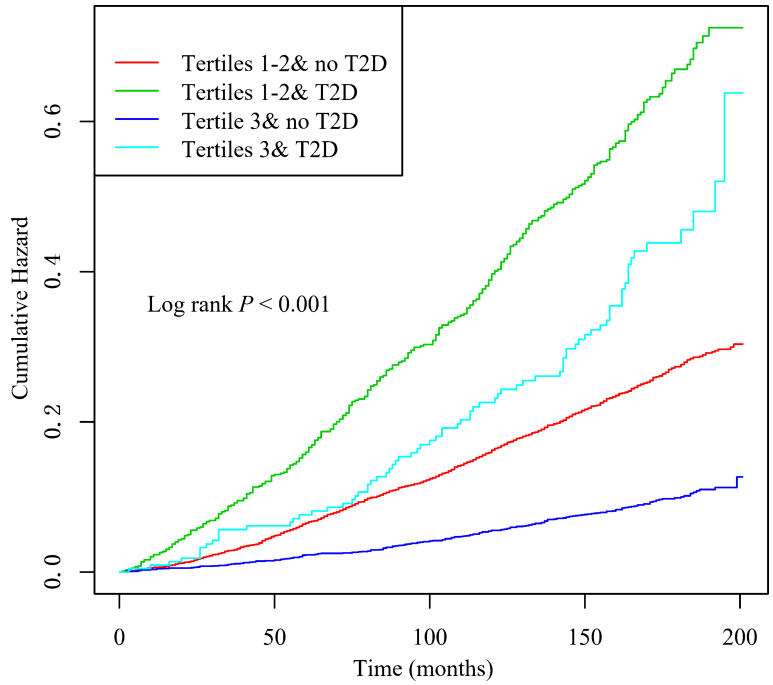

FIGURE 2
Kaplan–Meier curves of cumulative hazards of all-cause death by baseline leukocyte telomere length (T1–T2 vs T3) and type 2 diabetes status (with, without).

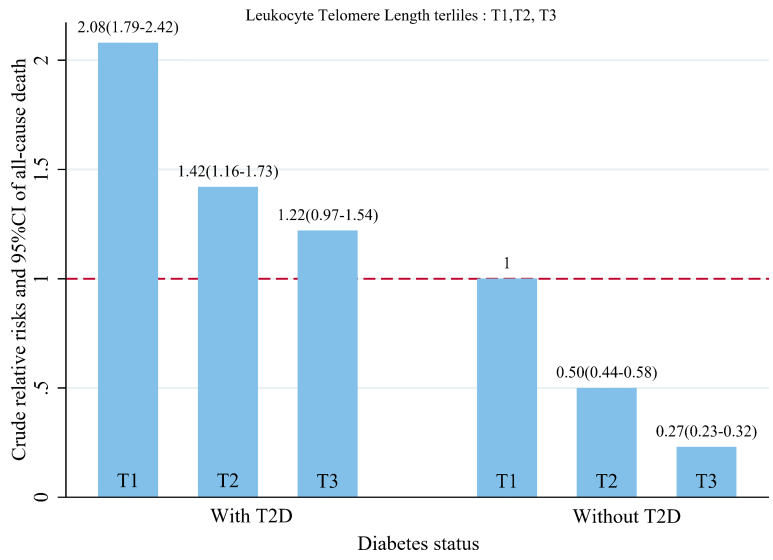

FIGURE 3
Dose–response relationship between baseline leukocyte telomere length quartiles and crude hazard ratios and 95%CI of all-cause death, stratified by status of T2D.

TABLE 3 Joint effects of baseline telomere length (Tertile 1-2 vs Tertile 3) and status of diabetes (Yes, No) on all-cause mortality.

Combined Groups		Non-adjusted	Adjust I	Adjust II
DM	telomere length (T/S ratio)			
No	Tertile 1-2	1 (Ref)	1 (Ref)	1 (Ref)
No	Tertile 3	0.37 (0.33, 0.42) <0.0001	0.85 (0.74, 0.97) 0.0178	0.86 (0.75, 0.98) 0.0240
Yes	Tertile 1-2	2.18 (1.91, 2.50) <0.0001	1.44 (1.26, 1.65) <0.0001	1.14 (0.95, 1.38) 0.1662
Yes	Tertile 3	1.57 (1.31, 1.89) <0.0001	1.63 (1.36, 1.96) <0.0001	1.34 (1.07, 1.68) 0.0101

Non-adjusted model adjust for: None.
Adjust I model adjust for: Age, sex, and smoking.
Adjust II model adjust for: Age, sex, smoking, cancer, hypertension, CVD, MetS, eGFR, albumin, and antidiabetic drug.

shorter telomeres and elevated probability of mortality in general population in previous studies that focused on older patients (27, 32). The possible explanation is that telomere shortening has telomeres have ahead presented among elderly individuals. Besides, considering the influence of other potential risk factors for mortality (such as myocardial infarction, malignancy), the independent effect of LTL on all-cause death becomes less significant. Glucose-induced oxidative stress and proinflammatory conditions may be involved in T2D-induced LTL shortening (33). It has confirmed that inflammation contributes to the loss of telomere length in cultured proliferative cells. Therefore, theoretically, telomere length is impacted by the number of replications and inflammation (34). Furthermore, in animal studies, it has established that hyperglycemia reduce endothelial cell nitric oxide production, contributed to inflammation and oxidative stress, and stimulated LTL shortening and vascular atherosclerotic processes (35, 36). In addition, oxidative stress is elevated both in leukocytes and pancreatic β-cells, which may lead to LTL aberrantly shortening of β-cell and dysfunction during progressive cell divisions in insulin secretion (37). Those persons with T2D are particularly prone to obesity, hyperglycemia, and chronic inflammation, which exacerbates the LTL shortening process while contributing to atherogenesis (38). Telomere shortening was related to T2D complications, such as diabetic nephropathy, and microalbuminuria, while telomere shortening appears to be weakened in individuals with fairly well controlled T2D (39). These studies showed that oxidative stress may contribute to the decline of telomeres and the development of T2D. These findings further support the results that regarding all-cause death the joint effect of T2D and elevated LTL is larger than the sum of their individual effects.

In this prospective cohort study, a nationally representative survey of US adults is used to examine the joint effect of T2D and long-term care on mortality from all causes. However, there are several shortcomings in this study that need to be addressed. Firstly, it is possible that the measurement of LTL at baseline does not reveal all behavioral changes during follow-up. Furthermore, although multiple factors were adjusted in different models, unmeasured confounders associated with T2D and LTL may influence the findings.

Conclusion

In a large survey conducted among US adults, it was found that the joint effect of TLT and T2D was larger than the sum of the independent effects on the risk of all-cause death. Participants with high TLT and diabetes had the highest risk of death compared with other groups.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: Publicly National Health and Nutrition Examination Survey dataset was analyzed in this study. They are publicly available at https://www.cdc.gov/nchs/nhanes/index.

Ethics statement

Ethical review and approval was not required for the study of human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients OR patients legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

BL and XZ contributed to the conception or design of the work. BL and YB contributed to the acquisition, analysis, or interpretation of data for the work. BL, YB, and XC drafted the manuscript. XZ critically revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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TYPE Original Research
PUBLISHED 02 December 2022
DOI 10.3389/fendo.2022.1008109

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Clinical Diabetes, a section of the journal Frontiers in Endocrinology

RECEIVED 31 July 2022
ACCEPTED 24 October 2022
PUBLISHED 02 December 2022

CITATION
Hirai H, Nagao M, Ohira T, Maeda M, Okazaki K, Nakano H, Hayashi F, Harigane M, Suzuki Y, Takahashi A, Sakai A, Kazama JJ, Hosoya M, Yabe H, Yasumura S, Ohto H, Kamiya K and Shimabukuro M (2022) Psychological burden predicts new-onset diabetes in men: A longitudinal observational study in the Fukushima Health Management Survey after the Great East Japan earthquake. *Front. Endocrinol.* 13:1008109. doi: 10.3389/fendo.2022.1008109

Psychological burden predicts new-onset diabetes in men: A longitudinal observational study in the Fukushima Health Management Survey after the Great East Japan earthquake

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Background: The burden of psychological distress and post-traumatic stress disorder (PTSD) has been suggested as a factor in developing type 2 diabetes mellitus. However, longitudinal features in psychological distress- and PTSD-related new-onset diabetes mellitus have not been thoroughly evaluated.

Methods: The association between probable depression and probable PTSD and the risk of developing new-onset diabetes mellitus was evaluated in a 7-year prospective cohort of evacuees of the Great East Japan Earthquake in 2011. Probable depression was defined as a Kessler 6 scale (K6) $\geq$ 13 and probable PTSD as a PTSD Checklist—Stressor-Specific Version (PCL-S) $\geq$ 44.

Results: The log-rank test for the Kaplan–Meier curve for new-onset diabetes mellitus was significant between K6 $\geq$ 13 vs. < 13 and PCL-S $\geq$ 44 vs. < 44 in men but not in women. In men, both K6 $\geq$ 13 and PCL-S $\geq$ 44 remained significant in the Cox proportional hazards model after multivariate adjustment for

10.3389/fendo.2022.1008109

established risk factors and disaster-related factors, including evacuation, change in work situation, sleep dissatisfaction, and education.

Conclusion: The post-disaster psychological burden of probable depression and probable PTSD was related to new-onset diabetes in men but not in women. In post-disaster circumstances, prevention strategies for new-onset diabetes might consider sex differences in terms of psychological burden.

KEYWORDS

disaster, psychological stress, post-traumatic stress disorder, depression, gender differences, type 2 diabetes mellitus 4

Introduction

Psychological distress has been reported to be a risk factor for developing type 2 diabetes mellitus (1–3). States of psychological distress, such as non-specific symptoms of stress, anxiety, depression, personal traits, and type of external or psychological stressors, might play various roles in the development of diabetes mellitus (3). There is evidence that depression is an independent risk factor for type 2 diabetes mellitus (4); however, the risk of non-specific symptoms of stress are equivocal (5–7). It is also less clear whether post-traumatic stress disorder (PTSD) is associated with a higher risk of developing type 2 diabetes mellitus (8).

Previous reports of sex differences in the development of diabetes associated with psychological distress yielded conflicting results; Eriksson et al. (9) observed associations in men and others (10–12) in women. To our knowledge, there are no robust longitudinal studies comparing sex differences in the effects of PTSD on new-onset diabetes mellitus (13–16). O'Donnell claimed that the predominance of PTSD studies in male veterans generates concerns about generalizability to non-military populations or other populations defined by sex (17).

The Great East Japan Earthquake and subsequent tsunami and Fukushima Daiichi nuclear disaster, which occurred in March 2011, caused a devastating catastrophe in East Japan, mostly affecting local residents. The Fukushima Health Management Survey was conducted to investigate the effects of long-term, low-dose radiation exposure caused by the accident to assess the physical and mental well-being of evacuees (18, 19). Among the potential health concerns that arose after the Great East Japan Earthquake were mental health problems, including post-traumatic stress response, chronic anxiety and guilt, ambiguous loss, family and community separation, and stigmatization (20). A recent meta-analysis reported a higher rate of new-onset diabetes mellitus among disaster survivors (21). However, the longitudinal effects of the psychological burden on the onset of diabetes have not been elucidated in this population.

We evaluated the association between probable depression and probable PTSD and the risk of developing new-onset diabetes mellitus and its sex differences in a 7-year prospective cohort of survivors of the Great East Japan Earthquake.

Methods

Study design and population

This study was part of the Fukushima Health Management Survey that targeted 123,314 people aged 40–74 years at the time of the earthquake and was officially registered as being from 13 administrative districts (villages, towns, and cities), which included the evacuation zone (18, 22). The administrative districts included an evacuation zone and a non-evacuation zone. The Fukushima health management survey includes four detailed annual surveys: thyroid ultrasound examination, comprehensive health checks, mental health and lifestyle surveys, and pregnancy and birth surveys (18). Among the participants who underwent a medical health check (n = 40,099) and those who received the mental health survey (n = 56,774) between July 2011 and November 2012, we selected 27,001 participants (men 11,493, women 15,508) who underwent the two surveys (Figure 1). After excluding patients with diabetes (n = 3,589), no follow-up examinations (n = 3,680), and missing data for diabetes diagnosis (n = 142), 19,590 participants were included in the full analysis set. The study protocol was approved by the Ethics Review Committee of Fukushima Medical University (#29064), and all participants provided written informed consent.

Mental health assessment

To assess participants' mental health status, we used the Kessler 6 scale (K6) (23) and PTSD Checklist—Stressor-Specific

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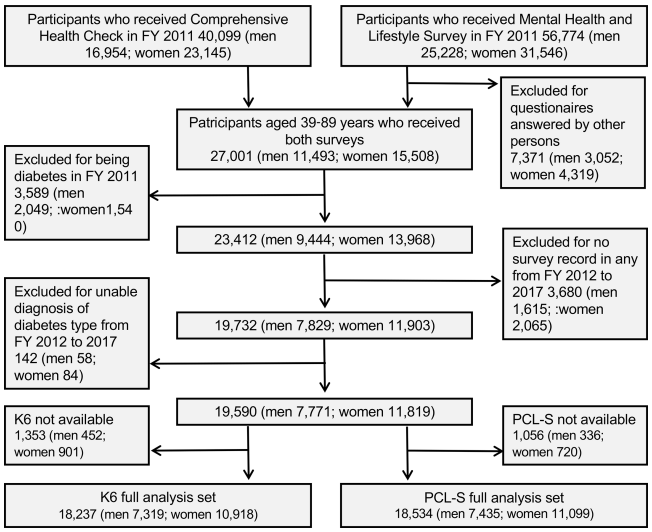

FIGURE 1
Enrollment flowchart of studied participants in Fukushima Health Management Survey. FY: fiscal year; K6: Kessler 6, PCL-S: PTSD Checklist Stressor-Specific Version.

Version (PCL-S) (24). The K6 scale used to measure non-specific mental health distress asked participants if they had experienced any of the 6 symptoms during the preceding 30 days: 'feeling so sad that nothing could cheer you up,' 'feeling nervous,' 'feeling hopeless,' 'feeling restless or fidgety,' 'feeling everything was an effort,' and 'feeling worthless.' Each question was scored using a 5-point Likert-type scale from 0 to 4, with higher scores indicating poorer mental health; thus, the total scores ranged from 0 to 24. The Japanese version of K6 has been previously validated (25, 26). Probable depression was defined as a K6 score of ≥ 13 (26). The PCL-S used to measure the traumatic symptoms caused by the Great East Japan Earthquake is a 17-item self-reported measure. We classified participants as having probable PTSD if their PCL-S total score was ≥ 44 (24). The Japanese version of the PCL-S was previously validated by the Fukushima Health Management Survey (27).

Diabetes- and disaster-related variables

General participant characteristics and diabetes- or disaster-related variables were assessed using self-report questionnaires. Smoking status was classified into three categories: never smoking, former smoking, and current smoking. Drinking status was classified as never drinking, former drinking, current drinking < 40 g/day in men and < 20 g/day in women, or current drinking ≥ 40 g/day in men and ≥ 20 g/day in women. Physical activity was classified into four categories: almost every day, 2–4 times/week, once/week, and almost never.

Participants were grouped into "evacuation" and "no evacuation." Participants with evacuation were defined as those from the evacuation zone or those from the non-evacuation zone who experienced living arrangements such as evacuation shelters and temporary housing. Post-disaster changes in work situations, including loss of employment and decrease in income, were answered with 'yes' or 'no.' Post-disaster sleep habits were classified into four categories: satisfied, slightly dissatisfied, quite dissatisfied, and very dissatisfied/have not slept. Educational attainment was divided into elementary school or junior high school (≤ 9 years of education), high school (10–12 years of education), vocational college or junior college (13–15 years of education), and university or graduate school (≥ 16 years of education) as described (28).

The laboratory data obtained from the participants included measurements of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γ-GT), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, fasting plasma glucose (FPG), and HbA1c. Diabetes was defined as FPG level ≥ 126 mg/dL, HbA1c level ≥ 6·5%, or self-reported use of antihyperglycemic agents. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or self-reported use of antihypertensive agents. Dyslipidemia was defined as an LDL-C level ≥ 140 mg/dL, triglyceride level ≥ 150 mg/dL, HDL cholesterol level < 40 mg/dL, or the use of lipid-lowering agents. Height (in stocking feet) and weight (wearing light clothing) were measured for each participant; BMI was calculated as weight (kg) divided by the

square of the height (m^2); overweight was defined as a BMI ≥ 25 kg/m^2.

Statistical analysis

Values are expressed as mean (standard deviation [SD] or confidence interval [95% CI]), number (%), or median (interquartile range [IQR], 25–75%]). Group comparisons were evaluated using Fisher's exact test for categorical variables and the Mann–Whitney *U* test or Student's *t*-test for continuous variables. Non-diabetic participants were categorized into K6 < 13 vs. K6 ≥ 13 or PCL-S < 44 vs. PCL-S ≥ 44 among both men and women. Kaplan-Meier survival curves for new-onset diabetes mellitus were constructed, and the probabilities were compared using a log-rank test between groups. Cox proportional hazard models were used to investigate the factors associated with new-onset diabetes mellitus. Factors evaluated included age (year), men (vs women), BMI < 18·5 (vs 18.5-24.9), BMI ≥ 25 (vs 18.5-24.9), hypertension, dyslipidemia, current smoking (vs no current smoking), former and current drinking < 40 g/day ≥ 40 g/day in men,< 20 g/day ≥ 20 g/day in women (vs never drinking), physical activity ≥ 2/week (vs <2/week), evacuation (vs no evacuation), change in work situation (vs no change in work situation), sleep satisfied (vs not dissatisfied), education ≥ 13 years (vs< 13), K6 ≥ 13 (vs < 13), and PCL-S ≥ 44 (vs < 44). Unadjusted, age- and sex-adjusted, and multivariate-adjusted hazard ratios (HR) and 95% CIs were calculated for all, men, and women. To investigate the effects of disaster-related variables on the associations between K6 ≥ 13 and PCL-S ≥ 44 and new-onset type diabetes mellitus, we constructed multivariate Cox proportional hazards models: Model 1: unadjusted; Model 2: Model 1+ age sex, and BMI (3 categories); Model 3: Model 2+ hypertension and dyslipidemia; Model 4: Model 3+ smoking habit, drinking habit, and physical activity; Model 5: Model 4+ evacuation; Model 6: Model 5 + sleep satisfied, Model 7: Model 6 + education ≥ 13 years, and Model 8: Model 7 + change in work situation. All statistical analyses were conducted using SPSS Statistics for Windows (version 23.0, IBM, Armonk, New York, NY, USA). All tests were two-sided, P < 0.05 was considered statistically significant.

Results

General characteristics

Men vs. women

The baseline characteristics of all men and women are shown in Table 1. A total of 19,590 participants showed a mean age of 62·5 (SD 10.8) years and 39·7% were men. Men had a lower median score in the K6 and PCL-S groups. Men were older and had a higher prevalence of BMI ≥ 25, hypertension, currentNew onset diabetes mellitus smoking, and regular exercise. Men had a lower prevalence of sleep dissatisfaction and a comparable rate of evacuation and change in work situation than women. Men had a higher fasting plasma glucose level but a slightly lower HbA1c level (men 5·3% vs. women 5·4%).

K6 < 13 vs. K6 ≥ 13

In all participants, the mean ages were comparable between K6 < 13 vs. K6 ≥ 13, and men were less in K6 ≥ 13 (42·0% vs. 29.4%). In men, the mean age was slightly lower in K6 ≥ 13, and BMI ≥ 25 was comparable between K6 < 13 and K6 ≥ 13. In women, the mean age was slightly higher in K6 ≥ 13, and BMI ≥ 25 was comparable. In both men and women, the prevalence of evacuation, change in work situation and sleep dissatisfied were higher in K6 ≥ 13.

PCL-S < 44 vs. PCL-S ≥ 44

In all patients, the mean age was older, and men were less in PCL-S ≥ 44. In men, the men age was older in PCL-S ≥ 44, and BMI ≥ 25 kg/m^2 was comparable between PCL-S < 44 and PCL-S ≥ 44. In both men and women, hypertension was higher in PCL-S ≥ 44. Changes in work situation and sleep dissatisfaction were higher in the PCL-S ≥ 44.

New-onset diabetes mellitus

After seven years of follow-up and a mean follow-up time of 4.4 years (86,609 person-years at risk), 1,699 new cases of type 2 diabetes were identified among 19,590 non-diabetic participants in FY 2011. The incidence of type 2 diabetes was 19·6 (/1,000 person-years) for all, 27·5 for men, and 14·7 for women (Table 1).

In men, diabetes incidence by age group was larger in K6 ≥ 13 than in K6 < 13 (Figure 2A) and in PCL-S ≥ 44 than in PCL-S < 44 (Figure 2E). In women, however, the incidence of diabetes was comparable between the K6 and PCL-S < 44 dichotomies (Figures 2B, F). Meanwhile, the mean values of K6 and PCL-S were comparable in FY 2011 between participants with or without new-onset diabetes mellitus, but 95% confidence intervals were larger in participants with new-onset diabetes mellitus in men and women (Figures 2C, D, G, H).

Kaplan–Meier survival curves for new-onset diabetes

The Kaplan–Meier curves for new-onset diabetes are shown in Figure 3. The log-rank test indicated a significant difference between K6 ≥ 13 and K6 < 13 in men (p = 0·014) but not in all and women (Figure 3A). There were significant differences between PCL-S ≥ 44 and PCL-S < 44 in all (p = 0·011), men (p = 0·001), and women (p = 0·041) (Figure 3B).

TABLE 1 General characteristics of participants at baseline.

					All			Men			Women			All			Men			Women		
	All	Men	Women	P value	K6 < 13	K6 ≥ 13	P value	K6 < 13	K6 ≥ 13	P value	K6 < 13	K6 ≥ 13	P value	PCL-S < 44	PCL-S ≥ 44	P value	PCL-S < 44	PCL-S ≥ 44	P value	PCL-S < 44	PCL-S ≥ 44	P value
Subjects, n (%)	19,590	7771 (39.7)	11819 (60.3)		15,528 (85.1)	2709 (14.9)		6523 (89.1)	796 (10.9)		9005 (82.5)	1913 (17.5)		14364 (77.5)	4170 (22.5)		6064 (81.6)	1371 (18.4)		8300 (74.8)	2799 (25.2)	
Age (years), mean (SD)	62.5 (10.8)	64.1 (10.6)	61.5 (10.8)	<0.001	62.0 (10.7)	62.0 (10.5)	0.996	63.7 (10.6)	62.9 (10.3)	0.052	60.7 (10.6)	61.6 (10.5)	0.001	61.6 (10.7)	63.5 (10.5)	<0.001	63.5 (10.6)	65.0 (10.4)	<0.001	60.3 (10.6)	62.8 (10.4)	<0.001
Men, n (%)					6,523 (42.0)	796 (29.4)	<0.001							6,064 (42.2)	1,371 (32.9)	<0.001						
K6 score, median (Q1-Q3)	5 (2-10)	4 (1-9)	6 (2-11)	<0.001	4 (1-8)	16 (14-19)	<0.001	3 (0-7)	16 (14-19)	<0.001	5 (2-8)	16 (14-19)	<0.001	4 (1-7)	12 (9-16)	<0.001	3 (0-6)	12 (8-16)	<0.001	5 (2-8)	13 (9-17)	<0.001
PCL score, median (Q1-Q3)	30 (22-41)	27 (20-39)	31 (23-43)	<0.001	27 (21-36)	53 (43-64)	<0.001	25 (20-35)	52 (43-63)	<0.001	28 (22-37)	54 (43-64)	<0.001	26 (20-33)	54 (48-62)	<0.001	24 (19-32)	53 (48-62)	<0.001	27 (21-34)	54 (48-63)	<0.001
New onset diabetes mellitus																						
Person•years, total	86,608	33,172	53,436		68,973	12,009		28,047	3,355		40,926	8,655		63,849	18,440		26,110	5,767		37,739	12,673	
Folow-up periods (years), mean	4.4	4.3	4.5		4.4	4.4		4.3	4.2		4.5	4.5		4.4	4.4		4.3	4.2		4.5	4.5	
Incidence cases, n	1,699	911	788		1,316	251		738	113		578	138		1,200	401		674	192		526	209	
Incidence rate (/1,000 persons•years)	19.6	27.5	14.7		19.1	20.9		26.3	33.7		14.1	15.9		18.8	21.7		25.8	33.3		13.9	16.5	
Anthropometry																						
Systolic blood pressure (mmHg), mean (SD)	131 (16.1)	134 (15.5)	129 (16.3)	<0.001	131 (16.1)	130 (15.9)	<0.001	134 (15.5)	133 (15.3)	0.258	129 (16.3)	128 (15.9)	0.122	131 (16.1)	131 (16.1)	0.436	133 (15.4)	134 (15.6)	0.461	129 (16.3)	129 (16.1)	0.017
Diastolic blood pressure (mmHg), mean (SD)	79 (10.2)	81 (9.9)	77 (10.1)	<0.001	79 (10.2)	78 (10.3)	<0.001	81 (10.0)	81 (10.0)	0.644	77 (10.1)	77 (10.2)	0.011	79 (10.2)	78 (10.3)	0.082	81 (9.9)	81 (10.2)	0.980	77 (10.1)	77 (10.2)	0.755
Body weight (kg), mean (SD)	58.5 (10.6)	65.3 (9.8)	54.1 (8.6)	<0.001	58.9 (10.6)	57.5 (10.8)	<0.001	65.5 (9.8)	66.2 (9.9)	0.066	54.2 (8.5)	53.9 (8.9)	0.269	58.9 (10.6)	57.9 (10.6)	<0.001	65.4 (9.7)	65.5 (10.2)	0.787	54.2 (8.5)	54.2 (8.7)	0.985
Body mass index (kg/m^2), mean (SD)	23.7 (3.3)	24.2 (3.0)	23.3(3.4)	<0.001	23.6 (3.3)	23.6 (3.5)	0.604	24.2 (3.0)	24.4 (3.1)	0.024	23.2 (3.4)	23.2 (3.6)	0.898	23.6 (3.3)	23.8 (3.4)	<0.001	24.2 (3.0)	24.4 (3.1)	0.005	23.2 (3.4)	23.5 (3.5)	<0.001
Body mass index (kg/m^2), n (%)				<0.001			0.103			0.211			0.379			0.003			0.005			0.005
Missing	8 (0.0)	2 (0.0)	6 (0.1)		5 (0.0)	3 (0.1)		2 (0.0)	0 (0.0)		3 (0.0)	3 (0.2)		6 (0.0)	2 (0.0)		2 (0.0)	0 (0.0)		4 (0.0)	2 (0.1)	
< 18.5	875 (4.5)	167 (2.1)	708 (6.0)		679 (4.4)	141 (5.2)		142 (2.2)	12 (1.5)		537 (6.0)	129 (6.7)		635 (4.4)	190 (4.6)		125 (2.1)	31 (2.3)		510 (6.1)	159 (5.7)	

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TABLE 1 Continued

					All			Men			Women			All			Men			Women		
	All	Men	Women	P value	K6 < 13	K6 ≥ 13	P value	K6 < 13	K6 ≥ 13	P value	K6 < 13	K6 ≥ 13	P value	PCL-S < 44	PCL-S ≥ 44	P value	PCL-S < 44	PCL-S ≥ 44	P value	PCL-S < 44	PCL-S ≥ 44	P value
18.5 - 25.0	12,510 (63.9)	4,680 (60.2)	7,830 (66.2)		9,966 (64.2)	1,745 (64.4)		3,930 (60.2)	465 (58.4)		6,036 (67.0)	1,280 (66.9		9,277 (64.6)	2,576 (61.8)		3,701 (61.0)	772 (56.3)		5,576 (67.2)	1,804 (64.5)	
≥ 25.0	6,197 (31.6)	2,922 (37.6)	3,275 (27.7)		4,878 (31.4)	820 (30.3)		2,449 (37.5)	319 (40.1)		2,429 (27.0)	501 (26.2)		4,446 (31.0)	1,402 (33.6)		2,236 (36.9)	568 (41.4)		2,210 (26.6)	834 (29.8)	
Blood measurements																						
Fasting plasma glucose (mg/dl), mean (SD)	97 (9.6)	99 (9.7)	95 (9.2)	<0.001	97 (9.6)	96 (9.7)	0.012	99 (9.7)	99 (10.1)	0.820	95 (9.1)	95 (9.2)	0.692	96 (9.5)	96 (9.8)	0.652	99 (9.7)	99 (9.9)	0.433	95 (9.1)	95 (9.4)	0.141
HbA1c (%), mean (SD)	5.4 (0.4)	5.3 (0.4)	5.4 (0.3)	0.016	5.3 (0.4)	5.4 (0.4)	0.339	5.3 (0.4)	5.4 (0.4)	0.455	5.4 (0.3)	5.4 (0.4)	0.668	5.3 (0.4)	5.4 (0.4)	0.029	5.3 (0.4)	5.4 (0.4)	0.390	5.3 (0.3)	5.4 (0.4)	0.056
HDL cholesterol (mg/dl), mean (SD)	61 (15.2)	56 (14.4)	64 (14.9)	<0.001	61 (15.3)	61 (15.2)	0.450	56 (14.5)	55 (13.5)	0.079	64 (14.9)	63 (15.2)	0.034	61 (15.3)	60 (15.1)	0.034	56 (14.5)	55 (14.0)	0.002	64 (14.9)	63 (14.8)	<0.001
LDL cholesterol (mg/dl), mean (SD)	127 (32.1)	123 (31.7)	130 (32.1)	<0.001	127 (32.0)	127 (32.7)	0.365	123 (31.7)	124 (32.8)	0.410	130 (32.0)	128 (32.6)	0.002	127 (32.0)	126 (32.1)	0.117	123 (31.8)	123 (31.3)	0.900	130 (31.9)	128 (32.3)	0.001
Tryglicerides (mg/dl), mean (SD)	113 (73.0)	128 (92.3)	103 (54.6)	<0.001	113 (72.9)	114 (80.3)	0.300	128 (90.6)	137 (117.3)	0.019	102 (54.3)	105 (55.7)	0.034	112 (72.8)	117 (78.1)	<0.001	127 (90.6)	134 (105.6)	0.003	101 (53.6)	108 (58.2)	<0.001
Comorbidities																						
Hypertension, n (%)	9,956 (50.9)	4,592 (59.1)	5,364 (45.5)	<0.001	7,731 (49.8)	1,363 (50.4)	0.617	3,816 (58.5)	471 (59.2)	0.687	3,915 (43.6)	892 (46.7)	0.013	7,006 (48.8)	2,260 (54.3)	<0.001	3,497 (57.7)	862 (62.9)	<0.001	3,509 (42.4)	1,398 (50.0)	<0.001
Dyslipidemia, n (%)	11,115 (56.8)	4,275 (55.0)	6,840 (58.0)	<0.001	8,780 (56.6)	1,558 (57.6)	0.359	3,603 (55.3)	445 (55.9)	0.737	5,177 (57.6)	1,113 (58.2)	0.591	8,071 (56.2)	2,453 (58.9)	0.002	3,355 (55.4)	760 (55.5)	0.940	4,716 (56.9)	1,693 (60.6)	<0.001
Psychosocial factors																						
Smoking habit, n (%)				<0.001			<0.001			0.107			0.016			<0.001			0.087			0.030
Missing	615 (3.1)	92 (1.2)	523 (4.4)		336 (2.2)	107 (3.9)		54 (0.8)	11 (1.4)		282 (3.1)	96 (5.0)		289 (2.0)	171 (4.1)		49 (0.8)	26 (1.9)		240 (2.9)	145 (5.2)	
Never smoking	12,037 (61.4)	2,089 (26.9)	9,948 (84.2)		9,440 (60.8)	1,787 (66.0)		1,742 (26.7)	226 (28.4)		7,698 (85.5)	1,561 (81.6)		8,715 (60.7)	2,700 (64.7)		1,603 (26.4)	398 (29.0)		7,112 (85.7)	2,302 (82.2)	
Fomer smoking	4,380 (22.4)	3,713 (47.8)	667 (5.6)		3,656 (23.5)	471 (17.4)		3,150 (48.3)	351 (44.1)		506 (5.6)	120 (6.3)		3,394 (23.6)	781 (18.7)		2,915 (48.1)	621 (45.3)		479 (5.8)	160 (5.7)	
Current smoking	2,558 (13.1)	1,877 (24.2)	681 (5.8)		2,096 (13.5)	344 (12.7)		1,577 (24.2)	208 (26.1)		519 (5.8)	136 (7.1)		1,966 (13.7)	518 (12.4)		1,497 (24.7)	326 (23.8)		469 (5.7)	192 (6.9)	
Drinking habit, n (%)				<0.001			<0.001			<0.001			<0.001			<0.001			<0.001			0.009
Missing	410 (2.1)	50 (0.6)	360 (3.0)		198 (1.3)	87 (3.2)		31 (0.5)	3 (0.4)		167 (1.9)	84 (4.4)		179 (1.2)	112 (2.7)		30 (0.5)	9 (0.7)		149 (1.8)	103 (3.7)	
Never drinking	9,928 (50.7)	1,832 (23.6)	8,096 (68.5)		7,730 (49.8)	1,495 (55.2)		1,510 (23.1)	206 (25.9)		6,220 (69.1)	1,289 (67.4)		7,122 (49.6)	2,255 (54.1)		1,414 (23.3)	335 (24.4)		5,708 (68.8)	1,920 (68.6)	

(Continued)

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TABLE 1 Continued

					All			Men			Women			All			Men			Women		
	All	Men	Women	P value	K6 < 13	K6 ≥ 13	P value	K6 < 13	K6 ≥ 13	P value	K6 < 13	K6 ≥ 13	P value	PCL-S < 44	PCL-S ≥ 44	P value	PCL-S < 44	PCL-S ≥ 44	P value	PCL-S < 44	PCL-S ≥ 44	P value
Fomer drinking	504 (2.6)	386 (5.0)	118 (1.0)		371 (2.4)	84 (3.1)		292 (4.5)	56 (7.0)		79 (0.9)	28 (1.5)		330 (2.3)	134 (3.2)		253 (4.2)	103 (7.5)		77 (0.9)	31 (1.1)	
Current drinking: Men < 40, Women < 20 g/day	6,657 (34.0)	3,934 (50.6)	2,723 (23.0)		5,527 (35.6)	751 (27.7)		3,368 (51.6)	347 (43.6)		2,159 (24.0)	404 (21.1)		5,127 (35.7)	1,243 (29.8)		3,120 (51.5)	646 (47.1)		2,007 (24.2)	597 (21.3)	
Current drinking: Men ≥ 40, Women 20 > g/day	2,091 (10.7)	1,569 (20.2)	522(4.4)		1,702 (11.0)	292 (10.8)		1,322 (20.3)	184 (23.1)		380 (4.2)	108 (5.6)		1,606 (11.2)	426 (10.2)		1,247 (20.6)	278 (20.3)		359 (4.3)	148 (5.3)	
Physical activity, n (%)				<0.001			<0.001			<0.001			0.130			<0.001			0.062			<0.001
Missing	472 (2.4)	172 (2.2)	300 (2.5)		263 (1.7)	52 (1.9)		100 (1.5)	15 (1.9)		163 (1.8)	37 (1.9)		244 (1.7)	107 (2.6)		97 (1.6)	35 (2.6)		147 (1.8)	72 (2.6)	
Almost every day	3,340 (17.0)	1,654 (21.3)	1,686 (14.3)		2,699 (17.4)	378 (14.0)		1,401 (21.5)	136 (17.1)		1,298 (14.4)	242 (12.7)		2,444 (17.0)	674 (16.2)		1,282 (21.1)	284 (20.7)		1,162 (14.0)	390 (13.9)	
2-4 times/week	4,803 (24.5)	1,862 (24.0)	2,941 (24.9)		3,760 (24.2)	655 (24.2)		1,563 (24.0)	185 (23.2)		2,197 (24.4)	470 (24.6)		3,389 (23.6)	1,122 (26.9)		1,421 (23.4)	363 (26.5)		1,968 (23.7)	759 (27.1)	
1 times/week	2,895 (14.8)	1,106 (14.2)	1,789 (15.1)		2,315 (14.9)	377 (13.9)		949 (14.5)	100 (12.6)		1,366 (15.2)	277 (14.5)		2,120 (14.8)	622 (14.9)		876 (14.4)	192 (14.0)		1,244 (15.0)	430 (15.4)	
Almost never	8,080 (41.2)	2,977 (38.3)	5,103 (43.2)		6,491 (41.8)	1,247 (46.0)		2,510 (38.5)	360 (45.2)		3,981 (44.2)	887 (46.4)		6,167 (42.9)	1,645 (39.4)		2,388 (39.4)	497 (36.3)		3,779 (45.5)	1,148 (41.0)	
Evacuation, n (%)	10,786 (55.1)	4,223 (54.3)	6,563 (55.5)	0.103	8,169 (52.6)	1,834 (67.7)	<0.001	3,404 (52.2)	555 (69.7)	<0.001	4,765 (52.9)	1,279 (66.9)	<0.001	7,447 (51.8)	2,734 (65.6)	<0.001	3,106 (51.2)	916 (66.8)	<0.001	4,341 (52.3)	1,818 (65.0)	<0.001
Change in work situation, n (%)	10,384 (56.6)	4,255 (57.2)	6,129 (56.2)	0.191	7,928 (53.7)	1,796 (71.0)	<0.001	3,436 (54.5)	584 (75.5)	<0.001	4,492 (53.1)	1,212 (68.9)	<0.001	7,172 (52.3)	2,700 (69.7)	<0.001	3,120 (53.1)	959 (73.7)	<0.001	4,052 (51.8)	1,741 (67.7)	<0.001
Sleep satisfaction, n (%)				<0.001			<0.001			<0.001			<0.001			<0.001			<0.001			<0.001
Missing	3,634 (18.6)	1,418 (18.2)	2,216 (18.7)		2,739 (17.6)	483 (17.8)		1,143 (17.5)	140 (17.6)		1,596 (17.7)	343 (17.9)		2,433 (16.9)	808 (19.4)		1,030 (17.0)	266 (19.4)		1,403 (16.9)	542 (19.4)	
Satisfied	5,345 (27.3)	2,679 (34.5)	2,666 (22.6)		4,847 (31.2)	214 (7.9)		2,469 (37.9)	85 (10.7)		2,378 (26.4)	129 (6.7)		4,702 (32.7)	424 (10.2)		2,390 (39.4)	194 (14.2)		2,312 (27.9)	230 (8.2)	
Slightly dissatisfied	7,380 (37.7)	2,659 (34.2)	4,721 (39.9)		6,077 (39.1)	849 (31.3)		2,275 (34.9)	249 (31.3)		3,802 (42.2)	600 (31.4)		5,691 (39.6)	1,384 (33.2)		2,128 (35.1)	444 (32.4)		3,563 (42.9)	940 (33.6)	
Quite dissatisfied	2,523 (12.9)	822 (10.6)	1,701 (14.4)		1,586 (10.2)	803 (29.6)		554 (8.5)	222 (27.9)		1,032 (11.5)	581 (30.4)		1,343 (9.3)	1,092 (26.2)		459 (7.6)	339 (24.7)		884 (10.7)	753 (26.9)	
Very dissatisfied	708 (3.6)	193 (2.5)	515 (4.4)		279 (1.8)	360 (13.3)		82 (1.3)	100 (12.6)		197 (2.2)	260 (13.6)		195 (1.4)	462 (11.1)		57 (0.9)	128 (9.3)		138 (1.7)	334 (11.9)	
Education, n (%)				<0.001			<0.001			0.012			<0.001			<0.001			<0.001			<0.001
Missing	728 (3.7)	265 (3.4)	463 (3.9)		476 (3.1)	88 (3.2)		187 (2.9)	26(3.3)		289 (3.2)	62 (3.2)		398 (2.8)	165 (4.0)		162 (2.7)	57(4.2)		236 (2.8)	108 (3.9)	

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TABLE 1 Continued

	All	Men	Women	P value	All		P value	Men		P value	Women		P value	All		P value	Men		P value	Women		P value
					K6 < 13	K6 ≥ 13		K6 < 13	K6 ≥ 13		K6 < 13	K6 ≥ 13		PCL-S < 44	PCL-S ≥ 44		PCL-S < 44	PCL-S ≥ 44		PCL-S < 44	PCL-S ≥ 44	
≤ 9 years	5,211 (26.6)	2,334 (30.0)	2,877 (24.3)		3,866 (24.9)	738 (27.2)		1,854 (28.4)	261 (32.8)		2,012 (22.3)	477 (24.9)		3,542 (24.7)	1,213 (29.1)		1,725 (28.4)	448 (32.7)		1,817 (21.9)	765 (27.3)	
≤ 12 years	9,644 (49.2)	3,709 (47.7)	5,935 (50.2)		7,763 (50.0)	1,385 (51.1)		3,170 (48.6)	380 (47.7)		4,593 (51.0)	1,005 (52.5)		7,235 (50.4)	2,051 (49.2)		2,947 (48.6)	652 (47.6)		4,288 (51.7)	1,399 (50.0)	
13-15 years	2,803 (14.3)	649 (8.4)	2,154 (18.2)		2,354 (15.2)	375 (13.8)		571 (8.8)	61(7.7)		1,783 (19.8)	314 (16.4)		2,158 (15.0)	576 (13.8)		524 (8.6)	113 (8.2)		1,634 (19.7)	463 (16.5)	
≥ 16 years	1,204 (6.1)	814 (10.5)	390 (3.3)		1,069 (6.9)	123 (4.5)		741 (11.4)	68(8.5)		328 (3.6)	55 (2.9)		1,031 (7.2)	165 (4.0)		706 (11.6)	101 (7.4)		325 (3.9)	64(2.3)	
≥ 13 years	4,007 (20.5)	1,463 (18.8)	2,544 (21.5)	<0.001	3,423 (22.0)	498 (18.4)	<0.001	1,312 (20.1)	129 (16.2)	0.009	2,111 (23.4)	369 (19.3)	<0.001	3,189 (22.2)	741 (17.8)	<0.001	1,230 (20.3)	214 (15.6)	<0.001	1,959 (23.6)	527 (18.8)	<0.001

Cox proportional hazards model for new-onset diabetes mellitus

The univariate and multivariate Cox proportional hazards models for new-onset diabetes are shown in Table 2.

In all K6 full analysis sets (Table 2A), multivariate-adjusted HR associated with new-onset diabetes was significant in age, men, BMI ≥ 25, hypertension, and dyslipidemia. In men, the multivariate-adjusted HR of age BMI ≥ 25, hypertension, and dyslipidemia were associated with new-onset diabetes. The multivariate-adjusted HR was significant in evacuation and K6 ≥ 13. The age- and sex-adjusted HR, but not multivariate-adjusted HR, was significant in change in work situation. In women, the multivariate-adjusted HR was significantly associated with age BMI ≥ 25, hypertension, and dyslipidemia, but not with evacuation, change in work situation, and K6 ≥ 13. HR in current smoking, current drinking, physical activity ≥ 2/week, and sleep satisfaction were not significantly associated with new-onset diabetes in men and women. In contrast, the multivariate-adjusted HR of education ≥ 13 years and sleep dissatisfied were not significant in men but were significantly low in women.

In all PCL-S full analysis sets (Table 2B), multivariate-adjusted factors associated with new-onset diabetes were age male sex, BMI ≥ 25, hypertension, dyslipidemia, and evacuation, but not PCL-S ≥ 44. In men, the multivariate-adjusted factors were age BMI ≥ 25, hypertension, dyslipidemia, and PCL-S ≥ 44. In women, multivariate-adjusted factors were age BMI ≥ 25, hypertension, and dyslipidemia but not PCL-S ≥ 44. The multivariate-adjusted HR of education ≥ 13 years and sleep dissatisfied were also significantly low in women.

Next, we evaluated the effects of disaster-related variables on the relationship between K6 ≥ 13, PCL-S ≥44, and new-onset type diabetes mellitus using univariate and multivariate Cox proportional hazards models (Table 3).

In men, the HR of K6 ≥ 13 remained significant after correcting for age and BMI in three categories (Model 2), hypertension and dyslipidemia (Model 3), smoking habit, drinking habit, physical activity (Model 4), evacuation (Model 5), sleep satisfied (Model 6), education ≥ 13 years (Model 7), and change in work situation (Model 8). In women, K6 ≥ 13 was not a significant factor in the unadjusted or multivariate-adjusted models.

In men, PCL-S ≥ 44 showed significant HRs after correction for all variables, including age BMI, hypertension, dyslipidemia, smoking habit, drinking habit, physical activity, evacuation, sleep satisfied, education ≥ 13 years, and change in work situation. However, in women, the adjusted PCL-S score ≥ 44 was not statistically significant in the multivariate-adjusted models.

Discussion

This study evaluated the 7-year longitudinal impact of probable depression and probable PTSD on new-onset

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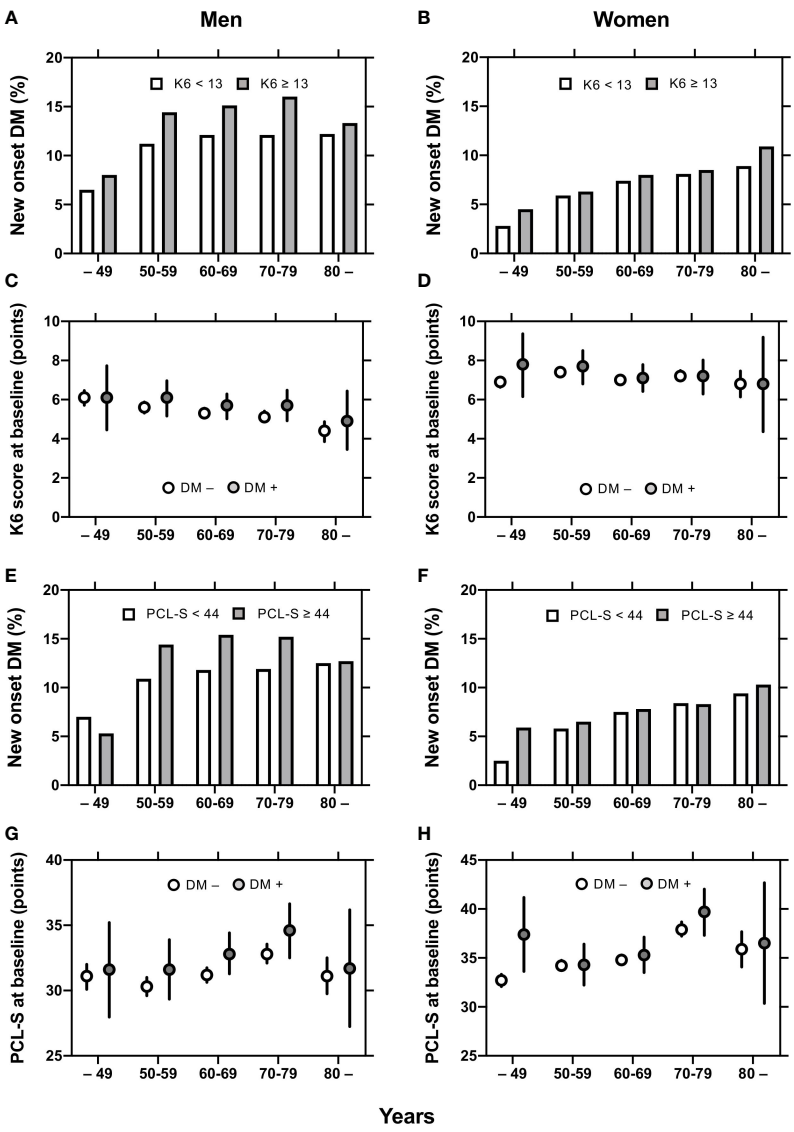

FIGURE 2
Mean K6 and PCL-S and incidence of new-onset diabetes in men and women. Diabetes incidence by age groups are shown in K6 < 13 (open columns) and K6 ≥ 13 (closed columns) participants **(A, B)** and in PCL-S < 44 (open columns) and PCL-S < 44 (closed columns) participants **(E, F)**. Mean values ± 95% confidence intervals [95% CI] of K6 **(C, D)** and PCL-S **(G, H)** by age groups are shown in participant with (closed circles) or without (open circles) new-onset diabetes mellitus. K6: Kessler 6, PCL-S: PTSD Checklist Stressor-Specific Version; DM: diabetes mellitus.

diabetes mellitus among Fukushima Health Management Survey participants who were survivors of the Great East Japan Earthquake. Two major findings were obtained in this study. First, among all participants, PCL-S ≥ 44 and K6 ≥ 13 were associated with the onset of type 2 diabetes mellitus (Table 3). Both K6 ≥ 13 and PCL-S ≥ 44 remained significant in the Cox proportional hazards model after multivariate adjustment for age, male sex, BMI ≥ 25, hypertension, dyslipidemia, smoking habit, drinking habit, physical activity, and evacuation but not after correction for sleep satisfied, education, and change in work situation (Table 3). Second, there was a sex difference in the associations between probable depression and probable PTSD on new-onset diabetes mellitus. The multivariate-adjusted Cox model indicated that K6 ≥ 13 and PCL-S ≥ 44 were determinants of new-onset diabetes mellitus in men, independent of evacuation, sleep satisfied, education, and change in work situation. Our results suggest that the post-disaster burden of probable depression and probable PTSD is causally related to new-onset diabetes in men but not in women.

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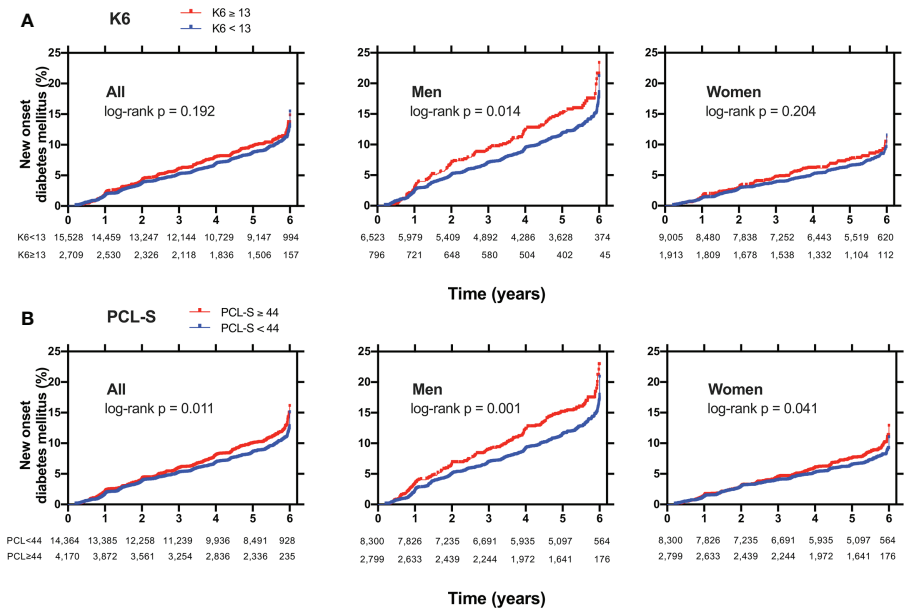

FIGURE 3
Kaplan Meier curves for new-onset diabetes mellitus in **(A)** participants with K6 < 13 (blue lines) or with K6 ≥ 13 (red lines) or in **(B)** participants with PCL-S < 44 (blue lines) or with PCL-S ≥ 44 (red lines). Non-diabetic participants were plotted for new-onset diabetes mellitus in all, men, and women. K6: Kessler 6, PCL-S: PTSD Checklist Stressor-Specific Version; DM: diabetes mellitus; P: p values calculated by log-rank test.

Association between probable depression and probable PTSD and new-onset diabetes mellitus

It has been implicated that both psychological distress (1–3) and PTSD (8) have causal effects on developing new diabetes mellitus. To our knowledge, however, the effects of psychological distress and PTSD, which are different responses to psychological stress, have never been compared with respect to the onset of diabetes. The current study found that PTSD-L ≥ 44 and K 6 ≥ 13 were both associated with the onset of type 2 diabetes mellitus (Table 3).

Previous reports have indicated that depression (4), but not general stress (5) and work stress (6, 7), is an independent risk factor for type 2 diabetes mellitus. Mezuk et al. reported that relative risk for new-onset diabetes associated with baseline depression was 1·60 (1·37–1·88) in the pooled analysis from 13 prospective studies (4). However, no significant association was found between work-related stress and the risk for type 2 diabetes based on a meta-analysis of seven prospective cohort studies (relative risk 0·94 [95% confidence interval 0.72–1.23]) (5).

It remains unclear whether PTSD is associated with a higher risk of developing type 2 diabetes mellitus (8). Vancampfort et al. demonstrated that the relative risk for type diabetes mellitus is 1·49 (95% CI 1·17–1·89, p = 0.001) (8). Three longitudinal case-control studies have been published until now (8). Miller–Archie et al. found a significant association between PTSD and diabetes in a logistic model (multivariate-adjusted odds ratio [AOR]1·28, 95% CI 1·14–1·44) in World Trade Center (WTC) survivors (n = 36,899) up to 11 years after the attack in 2001 (16). Pietrzak et al. reported that PTSD due to lifetime trauma exposures showed an AOR of 1·3 (1·07–1·52) for the diagnosis of diabetes mellitus in American adults (29). Roberts et al. showed that PTSD symptoms were dose-dependent with T2D incidence in a US longitudinal cohort of women (14). However, the authors equally acknowledged the limitations of self-reported diabetes diagnoses (8). This study is the first to demonstrate the relationship between PTSD and the onset of diabetes in a large cohort using a solid definition of diabetes (plasma glucose and HbA1c).

Overall, participants indicated that multivariate-adjusted HR of PCL-S ≥ 44 remained significant after correcting for age male sex, BMI ≥ 25, hypertension, dyslipidemia, smoking habit, drinking habit, and physical activity (Table 3), in agreement with the above studies (14, 16, 29). We obtained a new finding that the significance of HR disappeared in the Cox proportional hazards model with correction for covariates of evacuation, sleep dissatisfied, education, and change in work situation. This finding implies that these covariates underlie the cause-and-effect relationship between PTSD and new-onset diabetes. In our previous study, the the evacuation was a risk factor for a 4-year onset of diabetes among survivors of the Great East Japan Earthquake, which is consistent with the results of the current

TABLE 2 Factors associated with new-onset diabetes mellitus.

A. K6 full analysis set

		All (n = 18,237)									Men (n = 7,319)									Women (n = 10,918)								
		Unadjusted			Age- and sex-adjusted			Multivariate-adjusted			Unadjusted			Age- and sex-adjusted			Multivariate-adjusted			Unadjusted			Age- and sex-adjusted			Multivariate-adjusted		
Factors	Reference	HR	95%CI		HR	95%CI		HR	95%CI		HR	95%CI		HR			HR	95%CI		HR	95%CI		HR	95%CI		HR	95%CI	
Age (year)	Per year	1.03	1.02	1.03	1.02	1.02	1.03	1.01	1.01	1.02	1.01	1.01	1.02	1.01	1.01	1.02	1.01	1.00	1.02	1.02	1.03	1.04	1.03	1.02	1.04	1.01	1.003	1.02
Men	Women	1.90	1.72	2.09	1.78	1.61	1.97	1.64	1.45	1.85																		
Body mass index < 18.5	18.5 - 25.0	0.52	0.36	0.77	0.61	0.41	0.89	0.70	0.48	1.03	0.84	0.45	1.57	0.84	0.45	1.57	0.97	0.51	1.82	0.52	0.32	0.85	0.55	0.34	0.89	0.65	0.40	1.06
Body mass index ≥ 25.0	18.5 - 25.0	2.33	2.11	2.58	2.18	1.97	2.41	1.86	1.68	2.07	1.94	1.70	2.23	1.96	1.71	2.25	1.73	1.50	1.99	2.54	2.19	2.94	2.45	2.11	2.84	2.05	1.76	2.39
Hypertention	No hypertention	2.40	2.15	2.67	2.06	1.84	2.31	1.74	1.55	1.96	1.86	1.60	2.16	1.79	1.54	2.09	1.61	1.37	1.88	2.67	2.28	3.11	2.36	2.00	2.79	1.87	1.58	2.22
Dyslipidemia	No dyslipidemia	1.65	1.49	1.84	1.64	1.47	1.82	1.42	1.27	1.58	1.44	1.25	1.65	1.46	1.27	1.68	1.31	1.13	1.51	2.08	1.76	2.46	1.87	1.58	2.21	1.57	1.33	1.87
Current smoking	No current smoking	1.16	1.01	1.34	1.03	0.89	1.20	1.10	0.95	1.28	0.95	0.81	1.12	1.03	0.87	1.21	1.10	0.93	1.30	0.73	0.50	1.05	0.90	0.62	1.31	0.98	0.67	1.43
Fomer drinking	Never drinking	1.71	1.30	2.24	1.10	0.83	1.45	1.15	0.87	1.51	1.17	0.85	1.60	1.11	0.81	1.53	1.13	0.82	1.56	1.40	0.75	2.61	1.51	0.80	2.82	1.28	0.68	2.40
Current drinking	Never drinking	1.15	1.03	1.28	0.89	0.79	1.01	0.92	0.82	1.04	0.93	0.78	1.10	0.93	0.79	1.10	0.93	0.79	1.11	0.81	0.67	0.97	0.89	0.74	1.08	0.96	0.79	1.15
Current drinking: Men ≥ 40, Women 20 > g/day	Never drinking	1.32	1.13	1.54	0.97	0.82	1.15	0.95	0.80	1.14	1.01	0.83	1.23	1.05	0.86	1.29	0.992	0.81	1.22	0.50	0.31	0.81	0.62	0.38	1.02	0.69	0.42	1.13
Physical activity ≥ 2/week	< 2/week	1.16	1.05	1.28	0.95	0.85	1.06	0.98	0.88	1.09	1.06	0.93	1.22	0.96	0.83	1.11	0.98	0.84	1.13	1.18	1.02	1.37	0.95	0.82	1.11	0.99	0.85	1.16
Evacuation	No evacuation	1.17	1.05	1.29	1.21	1.09	1.34	1.14	1.03	1.27	1.23	1.07	1.41	1.25	1.09	1.43	1.16	1.000	1.34	1.12	0.96	1.30	1.16	1.000	1.35	1.12	0.96	1.31
Change in work situation	No change of job	1.07	0.97	1.19	1.15	1.04	1.28	1.05	0.94	1.17	1.18	1.03	1.36	1.25	1.08	1.44	1.15	0.99	1.33	0.94	0.80	1.09	1.04	0.89	1.21	0.95	0.81	1.11
Sleep satisfied	Sleep dissatisfied	0.91	0.80	1.04	0.82	0.72	0.94	0.89	0.77	1.02	0.996	0.81	1.22	0.97	0.79	1.18	1.08	0.87	1.34	0.74	0.62	0.89	0.72	0.60	0.86	0.74	0.61	0.90
Education ≥ 13 years	< 13	0.75	0.65	0.85	0.85	0.74	0.97	0.89	0.78	1.02	0.90	0.76	1.07	0.95	0.80	1.13	0.98	0.82	1.17	0.64	0.52	0.78	0.74	0.61	0.91	0.79	0.64	0.97
K6 ≥ 13	< 13	1.09	0.96	1.25	1.19	1.04	1.37	1.09	0.95	1.26	1.28	1.05	1.56	1.30	1.06	1.58	1.23	1.000	1.52	1.13	0.94	1.36	1.10	0.91	1.32	0.990	0.81	1.21

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TABLE 2 Continued

B. PCL-S full analysis set

		All (n = 18,534)									Men (n = 7,435)									Women (n = 11,099)								
		Unadjusted			Age- and sex-adjusted			Multivariate-adjusted			Unadjusted			Age- and sex-adjusted			Multivariate-adjusted			Unadjusted			Age- and sex-adjusted			Multivariate-adjusted		
Factors	Reference	HR	95%CI		HR	95%CI		HR	95%CI		HR	95%CI		HR			HR	95%CI		HR	95%CI		HR	95%CI		HR	95%CI	
Age (year)	Per year	1.03	1.02	1.03	1.02	1.02	1.03	1.01	1.01	1.02	1.01	1.01	1.02	1.01	1.01	1.02	1.01	1.00	1.02	1.03	1.03	1.04	1.03	1.03	1.04	1.01	1.00	1.02
Men	Women	1.88	1.71	2.08	1.76	1.59	1.94	1.64	1.45	1.85																		
Body mass index < 18.5	18.5 - 25	0.53	0.37	0.78	0.62	0.43	0.91	0.72	0.49	1.05	0.90	0.50	1.65	0.90	0.49	1.63	1.04	0.57	1.90	0.52	0.32	0.84	0.55	0.34	0.89	0.65	0.40	1.05
Body mass index ≥ 25	18.5 - 25	2.31	2.09	2.55	2.17	1.96	2.39	1.85	1.67	2.05	1.90	1.66	2.17	1.92	1.68	2.20	1.69	1.47	1.94	2.56	2.21	2.97	2.46	2.12	2.85	2.07	1.78	2.41
Hypertention	No hypertention	2.38	2.14	2.65	2.04	1.82	2.28	1.72	1.54	1.93	1.85	1.59	2.14	1.77	1.52	2.06	1.59	1.36	1.86	2.66	2.28	3.10	2.33	1.97	2.74	1.84	1.55	2.17
Dyslipidemia	No dyslipidemia	1.63	1.47	1.81	1.62	1.45	1.80	1.40	1.26	1.56	1.43	1.24	1.64	1.45	1.26	1.66	1.31	1.14	1.51	2.04	1.73	2.40	1.81	1.54	2.14	1.54	1.30	1.82
Current smoking	No current smoking	1.17	1.02	1.35	1.05	0.91	1.22	1.11	0.96	1.29	0.97	0.83	1.14	1.05	0.90	1.24	1.12	0.95	1.33	0.68	0.47	0.998	0.86	0.58	1.25	0.93	0.63	1.37
Fomer drinking	Never drinking	1.64	1.25	2.15	1.06	0.80	1.40	1.11	0.84	1.47	1.17	0.85	1.61	1.12	0.81	1.54	1.13	0.82	1.56	1.18	0.61	2.29	1.28	0.66	2.48	1.13	0.58	2.18
Current drinking	Never drinking	1.14	1.02	1.27	0.89	0.79	1.003	0.92	0.81	1.04	0.94	0.80	1.11	0.95	0.80	1.12	0.95	0.80	1.12	0.79	0.65	0.94	0.87	0.73	1.05	0.93	0.78	1.12
Current drinking: Men ≥ 40, Women 20 > g/day	Never drinking	1.31	1.12	1.52	0.97	0.82	1.15	0.95	0.80	1.13	1.02	0.84	1.25	1.07	0.88	1.31	1.01	0.83	1.24	0.50	0.31	0.80	0.62	0.39	1.000	0.68	0.42	1.10
Physical activity ≥ 2/week	< 2/week	1.15	1.04	1.27	0.93	0.84	1.03	0.96	0.86	1.06	1.06	0.93	1.22	0.95	0.83	1.10	0.97	0.84	1.12	1.15	0.99	1.33	0.92	0.78	1.07	0.95	0.82	1.11
Evacuation	No evacuation	1.16	1.05	1.28	1.20	1.09	1.33	1.13	1.02	1.26	1.22	1.06	1.40	1.24	1.08	1.42	1.15	0.99	1.32	1.12	0.96	1.29	1.16	1.00	1.34	1.12	0.96	1.30
Change in work situation	No change of job	1.07	0.96	1.18	1.14	1.03	1.27	1.05	0.94	1.16	1.17	1.02	1.34	1.24	1.07	1.42	1.12	0.97	1.30	0.93	0.80	1.09	1.04	0.89	1.21	0.96	0.82	1.13
Sleep satisfied	Sleep dissatisfied	0.91	0.80	1.04	0.82	0.72	0.94	0.89	0.77	1.02	0.997	0.82	1.22	0.97	0.79	1.18	1.10	0.89	1.36	0.74	0.62	0.89	0.72	0.61	0.87	0.73	0.61	0.89
Education ≥ 13 years	< 13	0.72	0.63	0.83	0.82	0.72	0.94	0.86	0.75	0.99	0.88	0.74	1.05	0.93	0.78	1.11	0.97	0.81	1.16	0.61	0.50	0.75	0.71	0.58	0.88	0.76	0.62	0.94
PCL-S ≥ 44	< 44	1.16	1.03	1.30	1.19	1.06	1.33	1.06	0.94	1.20	1.30	1.11	1.53	1.28	1.09	1.50	1.20	1.01	1.43	1.18	1.01	1.39	1.09	0.93	1.29	0.95	0.80	1.13

HR, hazard ratio; CI, confidential intervals.

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10.3389/fendo.2022.1008109

TABLE 3 Hazard ratio of K6 ≥ 13 or PCL-S ≥44 for new onset diabetes mellitus.

		K6 ≥ 13									PCL-S ≥ 44								
		All (n= 18,237)			Men (n=7,319)			Women (n=10,918)			All (n= 18,534)			Men (n=7,435)			Women (n=11,099)		
	Factors	HR	95%CI		HR	95%CI		HR	95%CI		HR	95%CI		HR	95%CI		HR	95%CI	
Model 1:	Unadjusted	1.09	0.96	1.25	1.28	1.05	1.56	1.13	0.94	1.36	1.16	1.03	1.30	1.30	1.11	1.53	1.18	1.01	1.39
Model 2:	+ Age sex and body mass index (3 categories)	1.19	1.04	1.36	1.27	1.04	1.55	1.11	0.92	1.34	1.15	1.03	1.29	1.24	1.06	1.46	1.06	0.90	1.25
Model 3:	+ Hypertension and dyslipidemia	1.18	1.03	1.35	1.28	1.05	1.56	1.10	0.91	1.32	1.14	1.02	1.28	1.24	1.05	1.45	1.05	0.89	1.23
Model 4:	+ Smoking habit, drinking habit, and physical activity	1.17	1.02	1.34	1.27	1.04	1.55	1.10	0.91	1.32	1.13	1.01	1.27	1.23	1.05	1.44	1.05	0.89	1.23
Model 5:	+ Evacuation	1.14	1.00	1.31	1.23	1.01	1.50	1.08	0.90	1.30	1.11	0.99	1.24	1.20	1.02	1.41	1.03	0.88	1.21
Model 6:	+ Sleep satisfied	1.10	0.95	1.27	1.26	1.02	1.55	0.99	0.81	1.20	1.07	0.95	1.21	1.22	1.03	1.45	0.95	0.80	1.13
Model 7:	+ Education ≥ 13 years	1.10	0.95	1.27	1.26	1.02	1.55	0.98	0.81	1.20	1.07	0.95	1.21	1.22	1.03	1.45	0.94	0.80	1.12
Model 8:	+ Change in work situation	1.09	0.95	1.26	1.23	1.00	1.52	0.99	0.81	1.21	1.06	0.94	1.20	1.20	1.01	1.43	0.95	0.80	1.13

study (30). As changes in the work situation (31) and sleep disorders (32, 33) are considered to be associated with new-onset diabetes independently of PTSD, the cause-and-effect relationship between PTSD and these covariates should be carefully interpreted.

To our knowledge, the current study is the first to show sex differences in the association between PTSD and new-onset diabetes. Our results also suggest that the post-disaster burden of probable depression and probable PTSD is causally related to new-onset diabetes in men but not in women.

Gender difference in the relationship between probable depression and probable PTSD and new-onset diabetes mellitus

Previous studies have reported that depression (1–3, 34, 35) and PTSD (8, 14, 36, 37) are factors in the development of diabetes mellitus in both men and women, but there are also reports of gender differences (9, 38).

Eriksson et al. found that the AOR for new-onset diabetes was 2·2 (95%CI 1·2–4·1) in men and 0·5 (0·2–1·2) in women in an 8–10 years cohort study comprised Swedish middle-aged 2,127 men and 3,100 women with baseline normal glucose tolerance, suggesting that psychological distress increases the risk of type 2 diabetes in Swedish men, but not in women (9). Kato et al. showed that the AOR for high stress compared with low stress was 1·36 (1·13–1·63) among men and 1·22 (0·98–1·51) among women (38). The effect of sex differences in PTSD on new-onset of diabetes mellitus remains largely unknown. One limited report for gender difference in the PTSD after the 911 attacks showed that male sex was not a risk factor for the association between PTSD and new-onset diabetes (AOR men 1·06 (0·96–1·17) vs. women 1·0 reference) (16).

Potential mechanisms underlying the difference in probable depression- or PTSD-related new-onset diabetes

In the present study, the proportion of women among K6 ≥ 13 and PCL ≥ 44 groups was 70.6% and 67.1%, respectively; thus 2·40 and 2·04 times higher than that of men. This is consistent with previous studies showing that the incidence of PTSD is approximately twice as high in women as in men (39). Although the prevalence of probable depression and probable PTSD was higher in women, it was not a factor in developing diabetes mellitus in women but in men. There are four potential explanations for the sex difference in depression- or PTSD-related new-onset diabetes.

First, the symptom levels for probable depression and probable PTSD may differ between men and women. K6 and PCL-S are self-reported questionnaires and could be subjective. According to Eriksson et al., women were more likely to experience distress symptoms and overreport them, while men were more likely to tolerate distress symptoms and underreport them (9). If this is the case, men with distress symptoms may have larger neuroendocrine changes when the distress symptoms are self-reported (9). This notion agrees with our

results showing that the frequencies of participants with probable depression or probable PTSD were lower in men, but a relationship between probable depression/PTSD and new-onset diabetes was present only in men.

Second, neuroendocrine networks, including the hypothalamic-pituitary-adrenal axis (HPA), oxidative stress, and sympathetic nerve activity during mental stress, can be modified, influenced, or both differentially in men and women (3, 39). The neuroendocrine network provides a structural and functional basis for interactions between the brain, hormones, and organs that allow individuals to respond to acute and chronic external stimuli (39). Trauma survivors with PTSD have a highly sensitized HPA axis characterized by decreased basal cortisol levels and increased negative feedback regulation of the HPA axis (40). The HPA axis is more sensitive and responds more strongly to acute stress in women than in men (41). Fonkoue et al. hypothesized that stress reactivity observed in men leads to a higher risk for new-onset diabetes *via* high levels of cortisol, while the lower cortisol response to stress observed in women stems from a hypo-reactivity of the HPA, which is associated with an increased risk for psychological distress and PTSD (39). Whether sex differences in the HPA are linked to sex differences in depression- and PTSD-related new-onset diabetes needs to be determined in future studies.

Third, the effects of probable depression and probable PTSD on physical activity and eating habits may differ between men and women. Physical inactivity and undesirable eating habits can result in obesity and a substantial risk of new-onset diabetes mellitus (42). Although correction of BMI could not abolish the impact of K6 ≥ 13 and PCL-S ≥ 44 on new-onset diabetes mellitus, sex differences in the distribution of abdominal and ectopic fat cannot be ruled out as a potential confounder for probable depression and probable PTSD-related new-onset diabetes.

Fourth, the association of psychological stress with employment rate, socioeconomic status, and education levels, which may differ between men and women, could be linked to gender difference in new-onset diabetes. In men, the age and sex-adjusted HR, but not multivariate-adjusted HR, was significant in change in work situation (Tables 2A, B). It has been reported that unemployment impairs mental health largely in men among evacuees of the Great East Japan Earthquake (43, 44). In contrast, the multivariate-adjusted HR of education ≥ 13 years was not significant in men but was significantly low in women. Collectively, change in work situation in men and education ≥ 13 years in women could be associated with gender difference in new-onset diabetes. Previous studies reported that higher education level was associated with lower diabetes risk (32, 45) in agreement with our finding in women. However, to our knowledge, there are no prior studies indicating gender difference in the association between education level and new-onset diabetes. We must wait for future studies and carefully interpret this phenomenon. The impact of socioeconomic status on diabetes onset can differ in men and women. However, we could not assess such relationship in this study because of a lack of individual socioeconomic sources. In men, the HR of K6 ≥ 13 and PCL-S ≥ 44 remained significant after correcting for psychosocial factors such as evacuation (Model 5), sleep satisfied (Model 6), education ≥ 13 years (Model 7), and change in work situation (Model 8). These results might support that probable depression and probable PTSD may be involved in onset of diabetes independently of the psychosocial factors measured in this study.

Strength and limitation of this study

Our study has several strengths. The most notable are the longitudinal design and large sample size. Because the relationship between psychological burden and diabetes is bi-directional (4), establishing the order in which events occur is crucial, and providing insights into causal mechanisms and processes can be achieved only in a prospective and longitudinal manner. The next strength of this study was the use of annual investigations for new-onset diabetes mellitus by using the definition of objective indices, fasting plasma glucose level, HbA1c, or use of antihyperglycemic agents, not self-reported diabetes mellitus. By using these strengths of methodology, our study is the first to confirm the difference in men and women and the difference in the impacts of probable depression and probable PTSD on new-onset diabetes. Our study had several limitations. First, the current analyses did not account for potential confounding effects of antidepressant/anti-anxiety medications (46). Second, we could not determine probable depression before the Great East Japan Earthquake. Third, the lack of information on BMI, physical activity, and dietary records during the study period may be an important limitation. Although the baseline BMI, physical activity, and drinking status were not strong confounders, an increase in BMI caused by physical inactivity and hyperphagia (36, 37) through probable depression may be a confounder for the onset of diabetes. Fourth, we could not determine the underlying mechanism of sex differences in psychological burden-related new-onset diabetes. As discussed above, attenuation in the neuroendocrine network might be linked to sex differences. Fifth, we could not differentiate between the stressors for the onset of diabetes. These populations were survivors of the Great East Japan Earthquake, including the subsequent tsunami and the Fukushima Daiichi nuclear disaster; therefore, we could not differentiate the source of psychological burdens, such as post-traumatic stress response, chronic anxiety and guilt, ambiguous loss, family and community separation, and stigmatization. The

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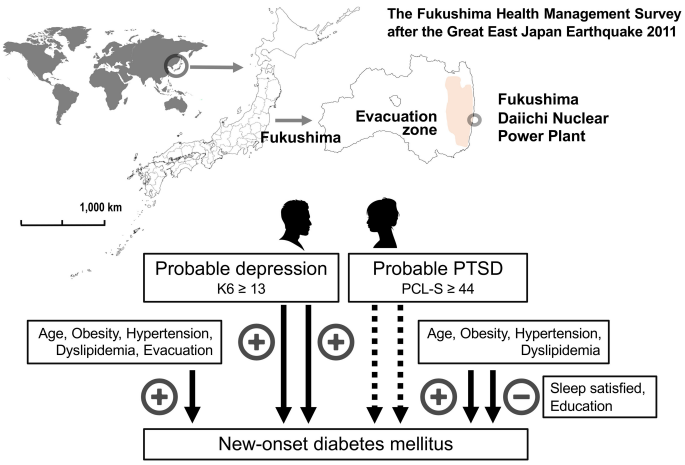

FIGURE 4
Graphic summary of the main findings of the article. The Fukushima Health Management Surve study targeted 123,314 people aged 40–74 years and was officially registered as being from 13 administrative districts at the time of the Great East Japan Earthquake 2011. Factors associated with new-onset diabetes mellitus in men and women were shown based on the Cox proportional hazards model after multivariate adjustment for established risk factors. Factors positively (+) and negatively (–) associated with new-onset diabetes mellitus were shown. Probable depression was defined as a Kessler 6 scale (K6) ≥ 13 and probable post-traumatic stress disorder (PTSD) as a PTSD Checklist—Stressor-Specific Version (PCL-S) ≥ 44.

radiation dose in the evacuation areas was substantially low, according to a report by the United Nations Scientific Committee on the Effects of Atomic Radiation (47). Therefore, the radiation-related direct effects on physical and mental health should be minimal, but the radiation-related psychological burden could be operative in the onset of diabetes. Sixth, it has been reported that objective measures are superior to subjective measures in assessing sleep as it relates to glycemic control (48, 49). We adopted satisfaction questionnaire for sleep assessment mainly for assessment of mental problems after the disaster and could not obtain objective measures such as sleep time primarily due to cost and questionnaire time. This may limit our interpretation on of the effects of sleep on onset of T2DM. Finally, we could not compare the incidence of type 2 diabetes between the participants in this study and the Japanese outside this area. Goto et al. estimated incidence rate of new-onset diabetes as 9.6 per 1000 person-years (95%CI 8.3-11.1) in pooled studies defining diabetes using laboratory data, not self-reported (50). The incidence rate of diabetes in the current study was all 19.6, men 27.5, and women 14.7 per 1000 person-years, suggesting that the incidence was largely higher in this cohort of participants. We need to find factors associated with this high-incident diabetes in future studies.

Conclusion

In a 7-year longitudinal study conducted after the Great East Japan Earthquake, we found that psychological burden and PTSD were significant determinants for the onset of type 2 diabetes mellitus in the multivariate-adjusted model, but not after correction for evacuation, change in work situation, or sleep dissatisfaction. In men, but not women, psychological burden and PTSD were determined for new-onset diabetes independently of evacuation, change in work situation, or sleep dissatisfaction, indicating that the post-disaster psychological burden of probable depression and probable PTSD is causally related to new-onset diabetes in men, but not in women. Therefore, a prevention strategy for new-onset diabetes should consider sex differences in post-disaster circumstances. A graphic summary ot this article was shown in Figure 4.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Review Committee of Fukushima Medical University (#29064). The patients/participants provided their written informed consent to participate in this study.

Author contributions

HH and MS contributed to the design of this study, conducted the analyses, and wrote the manuscript with inputs from all authors. MN performed the statistical analyses with input from TO, KO, HN, and FH. MN, TO, MM, KO, HH, FH, MHa, YS, AT, AS, JJK, MHo, HY, SY, HO, and KK were responsible for data collection and review of study procedures. All authors have read and approved the final version of the manuscript. MS is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the data integrity and accuracy of the data analysis. All authors contributed to the article and approved the submitted version.

Funding

This survey was conducted as part of Fukushima Prefecture's post-disaster recovery plans and was supported by the National Health Fund for Children and Adults Affected by the Nuclear Incident, Ministry of the Environment, Japan (MOEJ): fund number, n/a.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 16 February 2023
DOI 10.3389/fendo.2023.1083179

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Clinical Diabetes, a section of the journal Frontiers in Endocrinology

RECEIVED 28 October 2022
ACCEPTED 31 January 2023
PUBLISHED 16 February 2023

CITATION
Luo Q, Li N, Zhu Q, Yao X, Wang M, Heizhati M, Cai X, Hu J, Abulimiti A, Yao L, Li X and Gan L (2023) Non-dipping blood pressure pattern is associated with higher risk of new-onset diabetes in hypertensive patients with obstructive sleep apnea: UROSAH data.
Front. Endocrinol. 14:1083179.
doi: 10.3389/fendo.2023.1083179

Non-dipping blood pressure pattern is associated with higher risk of new-onset diabetes in hypertensive patients with obstructive sleep apnea: UROSAH data

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Objective: Impairment of circadian blood pressure (BP) patterns has been associated with cardiovascular risks and events in individuals with hypertension and in general populations, which are more likely to be found in obstructive sleep apnea (OSA). The aim of this study was to investigate the association of non-dipping BP pattern with new-onset diabetes in hypertensive patients with OSA, based on Urumqi Research on Sleep Apnea and Hypertension (UROSAH) data.

Materials and methods: This retrospective cohort study included 1841 hypertensive patients at least 18 years of age, who were diagnosed with OSA without baseline diabetes and had adequate ambulatory blood pressure monitoring (ABPM) data at enrollment. The exposure of interest for the present study was the circadian BP patterns, including non-dipping and dipping BP pattern, and the study outcome was defined as the time from baseline to new-onset diabetes. The associations between circadian BP patterns and new-onset diabetes were assessed using Cox proportional hazard models.

Results: Among 1841 participants (mean age: 48.8 ± 10.5 years, 69.1% male), during the total follow-up of 12172 person-years with a median follow-up of 6.9 (inter quartile range: 6.0-8.0) years, 217 participants developed new-onset diabetes with an incidence rate of 17.8 per 1000 person-years. The proportion of non-dippers and dippers at enrollment in this cohort was 58.8% and 41.2%, respectively. Non-dippers were associated with higher risk of new-onset diabetes compared with dippers (full adjusted hazard ratio [HR]=1.53, 95% confidence interval [CI]: 1.14-2.06, P=0.005). Multiple subgroup and sensitivity analyses yielded similar results. We further explored the association of systolic and diastolic BP patterns with new-onset diabetes separately, and found that diastolic BP non-dippers were associated with higher risk of new-onset diabetes (full adjusted HR=1.54, 95% CI: 1.12-2.10, P=0.008), whereas for systolic BP non-

dippers, the association was nonsignificant after adjusted the confounding covariates (full adjusted HR=1.35, 95% CI: 0.98-1.86, *P*=0.070).

Conclusions: Non-dipping BP pattern is associated with an approximately 1.5-fold higher risk of new-onset diabetes in hypertensive patients with OSA, suggesting that non-dipping BP pattern may be an important clinical implication for the early prevention of diabetes in hypertensive patients with OSA.

KEYWORDS

New-onset, diabetes, circadian blood pressure patterns, non-dipping, obstructive sleep apnea, hypertension

Introduction

The global number of adult patients with diabetes between 20 and 79 years reached 537 million and was responsible for 6.7 million deaths in 2021 (1). Among Chinese adults, the number of patients with diabetes was 111.6 million in 2019 and will reach 147 million in 2045 (2, 3). Early prevention for diabetes is pivotal to reduce the disease burden.

Obstructive sleep apnea (OSA), a condition characterized by intermittent hypoxia and sleep fragmentation due to a complete or partial collapse of the upper airway, is highly prevalent in parallel with the obesity epidemic trends in the general population (4), with estimated nearly one billion worldwide (5). OSA and hypertension (HTN) are highly prevalent conditions in the general population, approximately 50% of OSA patients noted to have HTN (6). Accumulating evidence has confirmed a strong association between OSA, HTN and diabetes (7–10). Shared mechanisms may involve enhanced sympathetic activity, oxidative stress, systemic inflammation, activation of the hypothalamic-pituitary-adrenal axis and alteration of circulating adipokines, induced by intermittent hypoxia and sleep fragmentation (4, 11, 12). In addition, enhanced sympathetic activity can alter circadian blood pressure (BP) rhythm resulting in a non-dipping BP pattern (11, 13), which was found to be increased by approximately 1.5 times likelihood in patients with OSA compared with non-OSA (14).

Emerging evidence has revealed that the non-dipping BP pattern is associated with adverse cardiovascular risks and events in both normal and HTN participants compared to the dipping pattern (15–18). Numerous cross-sectional studies have shown a high prevalence of non-dipping phenomenon in diabetes and even in early-stage diabetes (19–21). A recently prospective study with 21-year follow-up documented an independent association between non-dipping BP pattern and risk of new-onset diabetes in a randomly selected Finnish (n=449), originally middle-aged population with/without HTN (22). However, the longitudinal association between non-dipping pattern and the risk of developing new-onset diabetes in hypertensive patients with OSA remains unexplored.

While OSA and HTN have been substantiated to be associated with a higher risk of new-onset diabetes overall (4, 7–10, 23), non-dipping BP pattern may be a possible mechanism to accelerate the development of diabetes in hypertensive patients with OSA. Hence, we aimed to investigate the association between circadian BP patterns and new-onset diabetes based on Urumqi Research on Sleep Apnea and Hypertension (UROSAH) data.

Materials and methods

Study design and subjects

Data were obtained from the UROSAH study. The design and data collection of the UROSAH study have been described in detail elsewhere (24–26). Briefly, UROSAH is a single-center observational study to assess the association of OSA with long term cardiovascular outcomes in patients with HTN. Hypertensive patients aged ≥18 years who visited Hypertension Center between Jan 2011 and Dec 2013 were reviewed. In the current study, 1841 hypertensive patients who were diagnosed with OSA without baseline diabetes and had adequate ambulatory blood pressure monitoring (ABPM) data at enrollment were included, the patient recruitment flowchart is illustrated in Figure 1.

Ethical approval

The research was authorized by the Medical Ethics Committee of the People's Hospital of Xinjiang Uygur Autonomous Region (No. 2019030662) and was conducted in strict compliance with the ethical standards set forth in the Declaration of Helsinki and its subsequent amendments. Written informed consent was submitted by all patients or their legal relatives participating in this study.

Definitions at baseline

HTN was defined according to the "China guidelines for prevention and treatment of hypertension 2010": the resting systolic BP (SBP) of at least 140 mmHg and/or the resting diastolic BP (DBP) of at least 90 mmHg or the current use of antihypertensive drugs (27).

Smoking and drinking status were stratified into two levels: current (current smoking/drinking or quit within the past 1 year) and never or former (non-smokers/drinkers or those who quit more than 1 year).

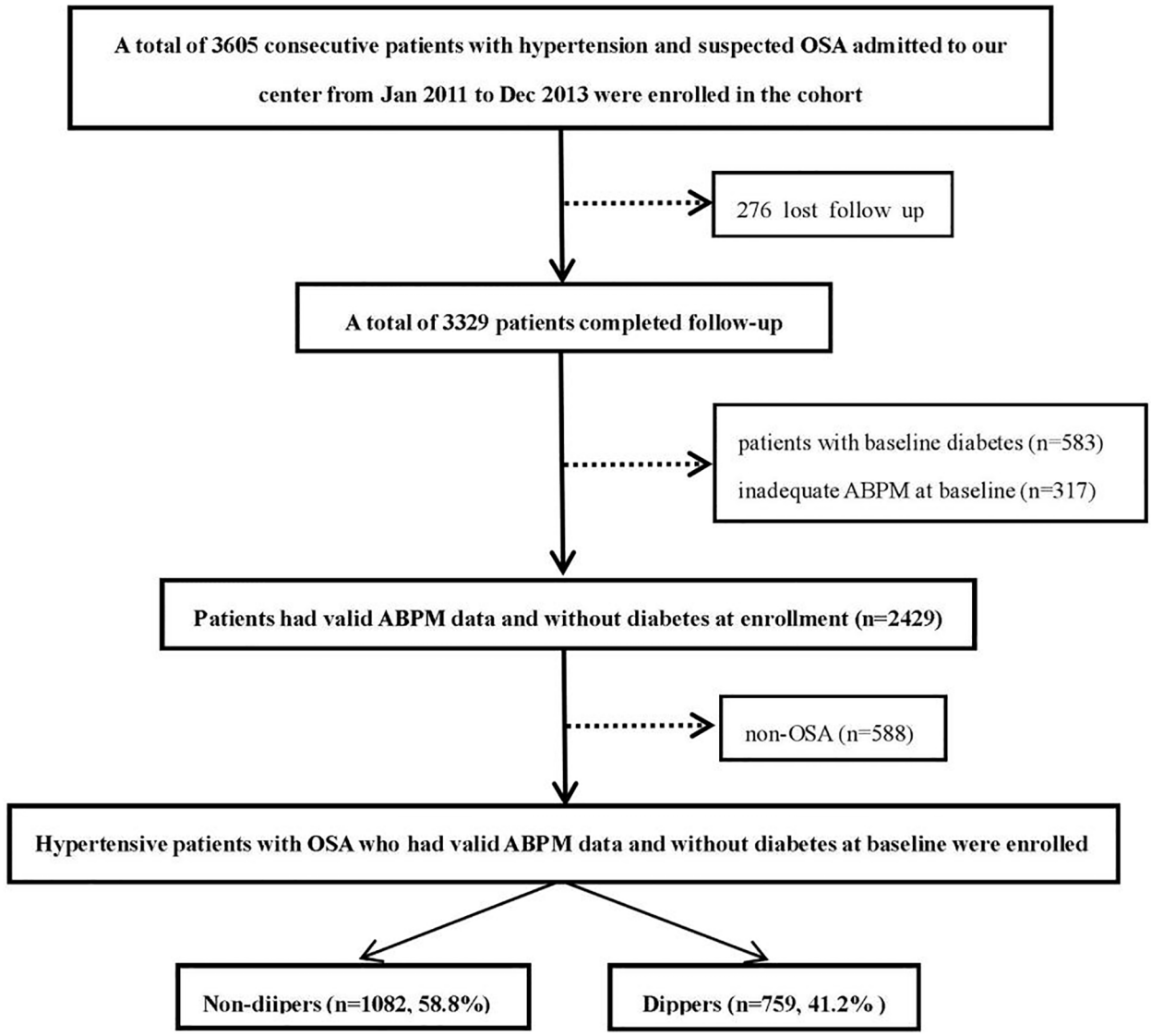

FIGURE 1
Study recruitment flowchart. OSA, obstructive sleep apnea; ABPM, ambulatory blood pressure monitoring.

The height and weight were measured and body mass index (BMI) was calculated by weight (kg)/height (m^2), obesity was defined as BMI≥28 kg/m^2 and overweight as 24 kg/m^2 ≤ BMI <28 kg/m^2 according to the Criteria of Weight for Adults of the health industry standard of China, WS/T 428–2013.

Baseline prediabetes included impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). IFG was defined if a fasting plasma glucose (FPG) ranged from 6.1 to less than 7.0 mmol/L, whereas 2-h glucose was less than 7.8 mmol/L; IGT was defined if 2-h glucose ranged from 7.8 to less than 11.0 mmol/L (28).

OSA was defined as an apnea-hypopnea index (AHI) ≥5 events per hour based on polysomnography (PSG) examination. Severity of OSA was defined as follows: mild OSA (5≤AHI<15 events per hour) and moderate-severe OSA (AHI≥15 events per hour) (5).

Regular continuous positive airway pressure (CPAP) treatment was defined as the use of CPAP therapy for more than 70% of nights throughout the follow-up period and no less than 4 hours per night.

Exposure of interest

The exposure of interest was the circadian BP patterns according to the ABPM parameters. Twenty-four-hour ABPM was performed at enrollment using an oscillometric recorder (Spacelabs 90217). Briefly, the cuff with appropriate size was fitted in the non-dominant arm. After device application, subjects were encouraged to follow their usual daily activity for the next 24 h. The device was programmed to automatically measure BP every 20 min during daytime (from 8:00 to 23:00) and every 30 min during nighttime (from 23:00 to 08:00). Patients were asked to go to bed at 23:00 and not to rise before 8:00 AM. Adherence to this schedule was checked from the diary card. Only ABPM reports with more than 70% of successful readings were considered valid and included in the analysis.

Dippers were participants whose nighttime (asleep) SBP and/or DBP fall ≥10% compared with that of daytime (awake), and those with nighttime SBP and DBP fall <10% were defined as non-dippers,

as indicated by the European Society of Hypertension (ESH) guidelines (29).

Elevated BP were according to the following criteria: SBP ≥130 mmHg and/or DBP ≥80 mmHg during 24-hour ABPM recording, SBP ≥135 mmHg and/or DBP ≥85 mmHg during daytime ABPM recording, SBP ≥120 mmHg and/or DBP ≥70 mmHg during nighttime ABPM recording (29).

Follow-up and outcome

All participants were followed up through medical records, outpatient and/or inpatient visits and telephone communication. The deadline for follow-up was January 2021. All events were certified by medical documents and confirmed by the clinical event committee. Details were described in previous studies (24–26).

The outcome for the present study was defined as time from baseline to new-onset diabetes, which was determined by the WHO criteria: diabetes was diagnosed if fasting plasma glucose was ≥7.0 mmol/L and/or 2-h plasma glucose was ≥11.1 mmol/L in 2-h oral glucose tolerance test, or if a person was use of antidiabetic medications.

Statistical analysis

The participants were divided into non-dippers and dippers according to their circadian BP patterns. Continuous variables were reported as mean ± standard deviation (SD) if normally distributed and as median and inter quartile range (IQR) if not. The differences between the two groups were compared using independent sample t-tests for normally distributed continuous variables and Mann-Whitney U-tests for non-normally distributed continuous variables. The categorical variables were presented as observed numbers and percentages and were compared among groups using Pearson's chi-squared test.

The incidence rate of new-onset diabetes was calculated by dividing the number of incident cases by the total follow-up duration (person-years). Cumulative hazards were estimated by Kaplan-Meier curves stratified by time-updated exposure (non-dippers versus dippers) by the log-rank test. To evaluate the validity of the proportional hazard assumption, the assumption was evaluated using the log-minus-log-survival function and was found to be valid. Cox proportional hazard regression models were used to compare the risk of new-onset diabetes across groups.

Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated, with dippers group as the reference group. Univariate Cox regression analysis was performed to select variables for adjustment (Supplementary Table 1). Before building the Cox regression model, we evaluated the covariance between variables according to the variance inflation factor (VIF) (Supplementary Table 1). Variables with VIF > 5 were considered inappropriate for inclusion in the multivariate Cox regression model. Thus, we eliminated 19 variables with multicollinearity, including waist circumference, waist-to-height ratio, serum creatinine, 24-h mean SBP, DBP, MAP and heart rate (HR), mean daytime SBP, MAP and HR, mean nighttime SBP, DBP, MAP and HR, elevated daytime BP, elevated nighttime BP, isolated elevated nighttime BP, SBP night-to-day ratios and DBP night-to-day ratios. Variables in multivariate analyses included traditional risk factors (model 1), further plus variables that gave p values <0.1 in the univariate analyses (model 2). We performed directed acyclic graphs (DAGs) by the program DAGitty for drawing and analyzed causal diagrams between non-dipping pattern and new-onset diabetes, to identify suitable minimally sufficient adjustment sets as full adjusted model (Figure 2, model 3).

Subgroup analyses with interaction tests were also conducted (Supplementary Table 2). Stratification of the study included gender (male and female), age (≥ 60 and < 60 years), BMI (≥ 28 and < 28 kg/m^2), current drinker (yes or no), hypertension duration (≥ 5 and < 5 years), AHI (≥ 15 and < 15 events/hour), angiotensin- converting-enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs) use (yes or no), and statins use (yes or no). Sensitivity analyses were performed in participants excluding baseline prediabetes, regular CPAP treatment, eGFR<60 mL/min/1.73 m^2, statins use and normal nighttime BP (Supplementary Table 2). A competing risk analysis with death was performed using the Fine-Gray model (Supplementary Table 3). Data were analyzed using SPSS statistical software (version 25.0, SPSS Inc., Chicago, Illinois) and R (version 4.2.1) software all analyses were two-tailed and *P* value<0.05 was statistically significant.

Results

Baseline characteristics

Overall, the proportion of non-dippers and dippers at enrollment in the present study was 58.8% and 41.2%, respectively. The characteristics of the study population at baseline are presented in Table 1. Compared with dippers, non-dippers had older age, less frequent male and current drinkers. No significant differences were found in BMI, waist circumference, waist-height ratio, office SBP and DBP levels, as well as in proportion of current smokers, obesity, overweight and baseline prediabetes between non-dippers and dippers.

As for clinical laboratory measurements, non-dippers had lower levels of total cholesterol, triglyceride (TG), serum potassium, eGFR and higher levels of serum sodium than dippers, no significant differences were found in levels of high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting blood glucose and serum creatinine between non-dippers and dippers.

For ABPM parameters, as expected, non-dippers had higher levels of mean 24-h and nighttime SBP, DBP and mean arterial pressure (MAP), more frequent elevated 24-h and nighttime BP, whereas lower levels of mean daytime SBP, DBP and HR, as well as less frequent elevated daytime BP than dippers.

Non-dippers received more calcium channel blockers (CCBs), diuretics and numbers of antihypertensive agents than dippers. No significant differences were found in the proportion of ACEI/ARBs and beta blockers use, as well as in major PSG parameters (e.g., AHI values, nadir SaO_2 levels and proportion of regular CPAP treatment) between non-dippers and dippers.

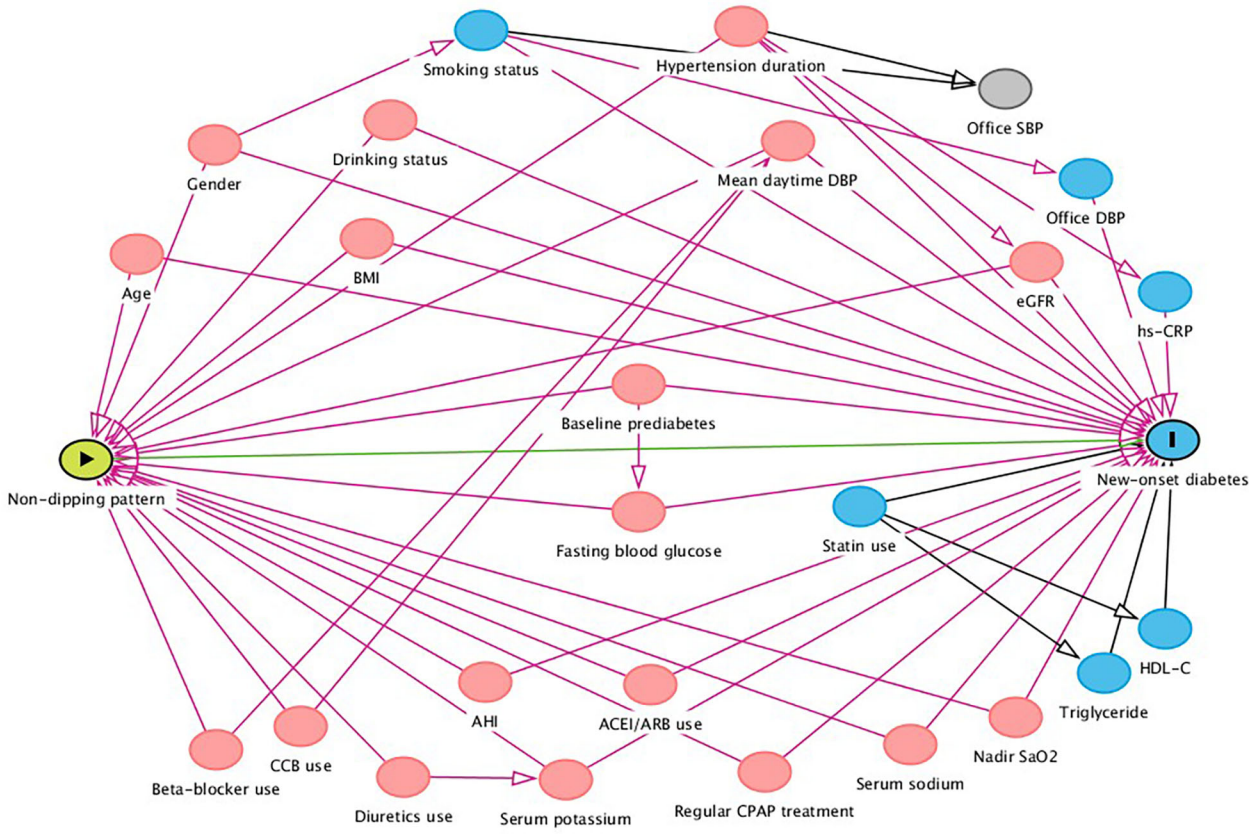

FIGURE 2
Directed acyclic graph of causal assumptions. Nodes represent variables and arrows represent causal associations. exposure outcome ancestor of exposure ancestor of outcome ancestor of exposure and outcome; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; AHI, apnea hypopnea index; SaO_2, oxygen saturation; CPAP, continuous positive airway pressure.

TABLE 1 Baseline characteristics for the total, non-dippers, and dippers.

Characteristics	Total	Non-dippers	Dippers	*P* value
Participants, n (%)	1841	1082	759	
Demographic characteristics				
Male, n (%)	1273 (69.1%)	727 (67.2%)	546 (71.9%)	0.030
Age, years	48.80 ± 10.47	49.40 ± 10.49	47.96 ± 10.40	0.004
Current smokers, n (%)	656 (35.6%)	372 (34.4%)	284 (37.4%)	0.180
Current drinkers, n (%)	644 (35.0%)	353 (32.6%)	291 (38.3%)	0.011
Body mass index, kg/m^2	28.23 ± 3.82	28.31 ± 3.90	28.11 ± 3.71	0.253
Waist circumference, cm	100.00 (93.00, 106.00)	100.00 (93.00, 107.00)	100.00 (94.00, 106.00)	0.739
waist-to-height ratio	0.58 (0.55, 0.63)	0.58 (0.55, 0.63)	0.58 (0.55, 0.62)	0.322
Obese, n (%)	891 (48.4%)	522 (48.2%)	369 (48.6%)	0.875
Overweight, n (%)	752 (40.8%)	446 (41.2%)	306 (40.3%)	0.698
Office SBP, mmHg	139.42 ± 19.42	139.37 ± 19.52	139.50 ± 19.27	0.892
Office DBP, mmHg	92.00 ± 13.94	92.19 ± 14.01	91.72 ± 13.84	0.471

(Continued)

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TABLE 1 Continued

Characteristics	Total	Non-dippers	Dippers	*P* value
Participants, n (%)	1841	1082	759	
Hypertension duration, years	3.0 (1.0, 8.0)	4.0 (1.0, 8.0)	3.0 (0.8, 7.0)	0.007
Baseline prediabetes, n (%)	239 (12.9%)	146 (13.5%)	93 (12.3%)	0.436
Clinical laboratory measurements				
Total cholesterol, mmol/L	4.54 ± 1.19	4.50 ± 1.02	4.61 ± 1.23	0.033
Triglyceride, mmol/L	2.08 ± 1.50	2.02 ± 1.36	2.17 ± 1.65	0.031
HDL-C, mmol/L	1.11 ± 0.30	1.12 ± 0.31	1.10 ± 0.28	0.308
LDL-C, mmol/L	2.66 ± 0.79	2.65 ± 0.81	2.67 ± 0.76	0.587
Fasting blood glucose, mmol/L	4.85 ± 0.63	4.83 ± 0.60	4.87 ± 0.66	0.138
Serum potassium, mmol/L	3.91 ± 0.34	3.88 ± 0.34	3.96 ± 0.34	<0.001
Serum sodium, mmol/L	140.69 ± 2.38	140.79 ± 2.50	140.56 ± 2.20	0.036
hs-CRP, mg/mL (M, IQR)	1.95 (1.95, 3.62)	2.04 (0.98, 3.71)	1.87 (0.89, 3.50)	0.053
Serum creatinine, umol/L	77.07 ± 20.00	77.23 ± 21.26	76.84 ± 18.03	0.673
eGFR, mL/min/1.73 m^2	90.18 ± 19.26	89.45 ± 18.92	91.24 ± 19.70	0.049
ABPM parameters				
Mean 24-h SBP, mmHg	133.16 ± 15.29	134.64 ± 15.56	131.05 ± 14.66	<0.001
Mean 24-h DBP, mmHg	85.61 ± 10.74	86.57 ± 11.00	84.23 ± 10.22	<0.001
24-h MAP, mmHg	100.49 ± 12.87	101.88 ± 12.98	98.51 ± 12.45	<0.001
Mean 24-h HR, bpm	75.63 ± 9.05	75.39 ± 9.27	75.96 ± 8.71	0.180
Mean daytime SBP, mmHg	136.40 ± 15.61	135.78 ± 15.75	137.29 ± 15.38	0.040
Mean daytime DBP, mmHg	88.32 ± 23.04	87.34 ± 11.11	89.72 ± 33.30	0.028
Daytime MAP, mmHg	102.68 ± 13.21	102.50 ± 13.00	102.93 ± 13.44	0.492
Mean daytime HR, bpm	79.81 ± 9.54	79.27 ± 9.63	80.60 ± 9.35	0.003
Mean nighttime SBP, mmHg	128.22 ± 16.88	133.47 ± 16.50	120.74 ± 14.43	<0.001
Mean nighttime DBP, mmHg	81.98 ± 11.65	85.57 ± 11.42	76.86 ± 9.94	<0.001
Nighttime MAP, mmHg	97.04 ± 13.79	101.14 ± 13.53	91.10 ± 11.89	<0.001
Mean nighttime HR, bpm	68.16 ± 8.89	68.48 ± 8.95	67.70 ± 8.79	0.064
Elevated 24-h BP, n (%)	1416 (76.9%)	858 (79.3%)	558 (73.5%)	0.004
Elevated daytime BP, n (%)	1272 (69.1%)	724 (66.9%)	548 (72.2%)	0.016
Elevated nighttime BP, n (%)	1649(89.6%)	1032 (95.4%)	617 (81.3%)	<0.001
Isolated elevated nighttime BP, n (%)	561 (30.5%)	416 (38.4%)	145 (19.1%)	<0.001
SBP night-to-day ratios	0.94 ± 0.07	0.98 ± 0.05	0.88 ± 0.04	<0.001
DBP night-to-day ratios	0.93 ± 0.08	0.98 ± 0.05	0.87 ± 0.05	<0.001
Prescribed medication, n (%)				
Numbers of antihypertensive drugs				
None, n(%)	167 (9.1%)	88 (8.1%)	79 (10.4)%)	0.094
1, n (%)	528 (28.7%)	288 (26.6%)	240 (31.6%)	0.019
2, n (%)	999 (54.3%)	608 (56.2%)	391 (51.5%)	0.047
3, n (%)	147 (8.0%)	98 (9.1%)	49 (6.5%)	0.043

(Continued)

TABLE 1 Continued

Characteristics	Total	Non-dippers	Dippers	*P* value
Participants, n (%)	1841	1082	759	
ACEI/ARB users, n (%)	894 (48.6%)	515 (47.6%)	379 (49.9%)	0.323
Calcium channel blocker users, n (%)	1353 (73.5%)	829 (76.6%)	524 (69.0%)	<0.001
Beta blocker users, n (%)	177 (9.6%)	104 (9.6%)	73 (9.6%)	0.997
Diuretic users, n (%)	284 (15.4%)	185 (17.1%)	99 (13.0%)	0.018
Statis users, n (%)	625 (33.9%)	365(33.7%)	260(34.4%)	0.816
PSG parameters				
AHI, events/hour	19.00 (10.35, 31.25)	19.30 (10.50, 31.60)	18.60 (10.00, 30.10)	0.196
Moderate-severe OSA, n (%)	1025 (58.5%)	618 (59.8%)	407 (56.7%)	0.190
Nadir SaO_2, %	80 (75, 84)	80 (75, 83)	80 (76, 84)	0.123
Mean SaO_2, %	91.86 ± 3.66	91.76 ± 3.60	92.00 ± 3.73	0.183
Regular CPAP treatment, n (%)	49 (2.7%)	29 (2.7%)	20 (2.6%)	0.953

Non-normally distributed variables are expressed as the median (inter quartile range). All other values are expressed as mean ± SD or n, %.
SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; IQR, inter quartile range; eGRF, estimated glomerular filtration rate; APBM, ambulatory blood pressure monitoring; MAP, mean arterial pressure; HR, heart rate; bpm, beats per minute; BP, blood pressure; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; PSG, polysomnography; AHI, apnea hypopnea index; OSA, obstructive sleep apnea; SaO_2, oxygen saturation; CPAP, continuous positive airway pressure.

Risk of new-onset diabetes in groups by non-dippers and dippers

Among 1841 participants (mean age: 48.8 ± 10.5 years, 69.1% male), during the total follow-up of 12172 person-years with a median follow-up of 6.9 (inter quartile range: 6.0-8.0) years, 217 participants developed new-onset diabetes with an incidence rate of 17.8 per 1000 person-years. Non-dippers experienced a higher cumulative hazard of new-onset diabetes than dippers during the follow-up period (*P*=0.0019 for log-rank test; Figure 3A). In univariate cox regression analysis (Supplementary Table 1), BMI, waist circumference, waist-to-height ratio, baseline prediabetes, TG, HDL-C, fasting blood glucose, statins use, AHI and nadir SaO_2 were associated with higher risk of new-onset diabetes. Apart from mean daytime DBP, SBP night-to-day ratios and DBP night-to-day ratios, no other ABPM parameter showed an association with new-onset diabetes.

Three multivariate models were performed through the following sequential adjustments: model 1 adjusted for traditional risk factors, including age, gender, drinking status, smoking status, BMI, office SBP, office DBP, hypertension duration and baseline prediabetes. Model 2 included covariates in Model 1 and further adjusted for variables that gave p values <0.1 in the univariate analyses and no multicollinearity, including TG, HDL-C, fasting blood glucose, mean daytime DBP, ACEIs/ARBs use, CCBs use, statins use, AHI and nadir SaO_2. Model 3 (full adjusted model) was based on minimal sufficient adjustment sets for estimating the total effect of non-dipping pattern on new-onset diabetes identified by DAG (Figure 2), including age, gender, drinking status, hypertension duration, baseline prediabetes, BMI, fasting blood glucose, eGFR, serum potassium, serum sodium, mean daytime DBP, ACEI/ARBs use, AHI, nadir SaO_2, and regular CPAP treatment. Non-dippers showed an increased risk for new-onset diabetes compared with dippers in crude model with an unadjusted HR of 1.57 (95% CI 1.18-2.09, *P*=0.002). The association remained consistently in adjusted models (full adjusted HR=1.53, 95% CI: 1.14-2.06, *P*=0.005) (Table 2).

We also explored association of systolic and diastolic BP patterns with new-onset diabetes separately (Figures 3B, C), and found that DBP non-dippers were associated with new-onset diabetes both in crude model (unadjusted HR=1.47, 95% CI:1.09-2.00, *P*=0.013) and adjusted models (full adjusted HR=1.54, 95%CI:1.12-2.10, *P*=0.008), whereas for SBP non-dippers, the association was only significantly in crude model (unadjusted HR=1.40, 95% CI: 1.02-1.92, *P*=0.036), after adjusted the aforementioned covariates, the association was nonsignificant (full adjusted HR=1.35, 95% CI: 0.98-1.86, *P*=0.070) (Table 2).

Subgroup and sensitivity analysis

In subgroup analysis, as shown in Table 3, compared with dippers, non-dippers exhibited higher risk for new-onset diabetes in participants whom were male, age<60 years, non-obese, current drinker, hypertension duration<5 years, moderate-severe OSA, no use of ACEI/ARBs and statins. None of above variables, substantially altered the association between non-dipping pattern and risk of new-onset diabetes (*P* for all interaction > 0.05).

Sensitivity analysis showed that the association of non-dipping BP pattern with the risk of new-onset diabetes didn't change in participants excluding baseline prediabetes, regular CPAP treatment, eGFR<60 mL/min/1.73 m^2, statins use and normal nighttime BP (Supplementary Table 2). We also performed a competing risk analysis with death as a competing event. Sub-distribution HRs for non-dipping pattern and new-onset diabetes after competing risk analysis are presented in Supplementary Table 3. The association between non-dipping pattern and new-onset diabetes remained significant in the Fine Gray model.

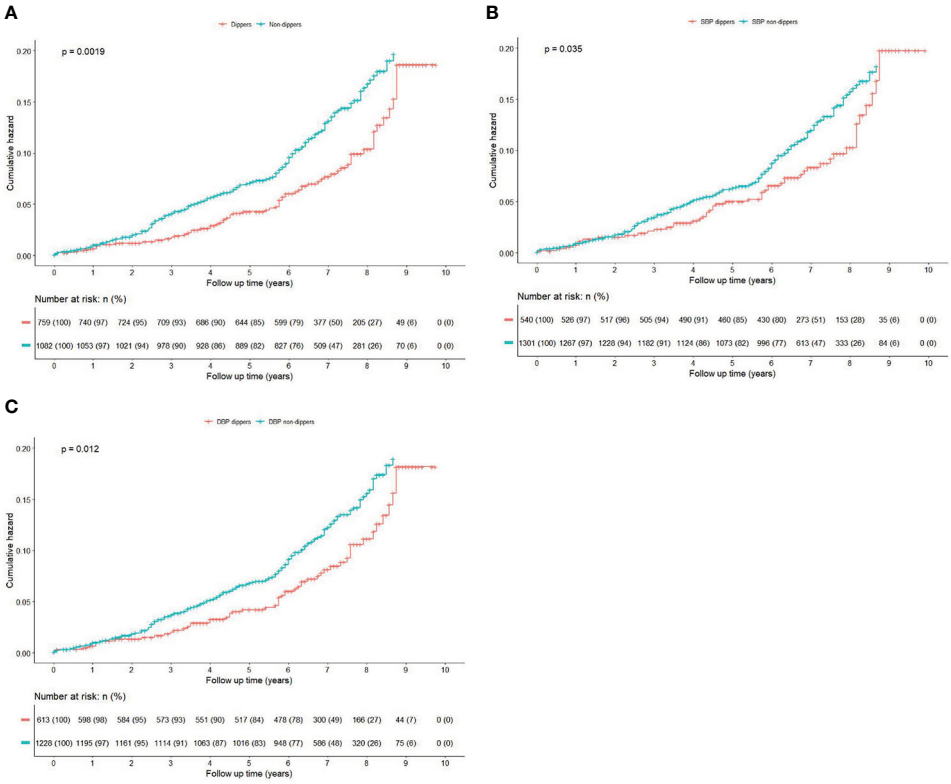

FIGURE 3
(Color online) Kaplan-Meier curves for the cumulative risk of new-onset diabetes by dipping and non-dipping pattern during the follow-up. Kaplan-Meier curves were compared with the log-rank test. **(A)** BP non-dippers vs dippers; **(B)** Systolic BP non-dippers vs dippers; **(C)** Diastolic BP non-dippers vs dippers.

Discussion

The current study is, to the best of our knowledge, the first to explore the association of nocturnal BP patterns with new-onset diabetes in a relatively large cohort of hypertensive patients with OSA. Our findings suggest that non-dippers, despite having similar levels of office SBP, DBP, and even lower mean daytime SBP and DBP compared to dippers, are associated with a higher risk of new-onset diabetes in hypertensive patients with OSA.

ABPM can assess circadian BP patterns over a 24-hour period and provides more useful prognostic information than clinic measurements of BP. The proportion of non-dippers at enrollment in the current cohort was as high as 58.8%, which is consistent with previous studies. A meta-analysis involving 1562 patients with OSA and 957 non-OSA controls from 14 studies revealed that the prevalence of non-dipping patterns in patients with OSA varied widely from 36.0% to 90.0% and non-OSA from 33.0% to 69.0%, depending on demographic or clinical characteristics, definitions of OSA and non-dipping phenotypes (14).

The dipping phenomenon occurs when lying recumbent due to lower leg fluid shifts in the rostral direction, increasing carotid intravascular fluid volume and triggering carotid baroreceptors to reflexively reduce sympathetic nervous activity (SNA), thus causing a nocturnal BP dipping. The enhanced SNA caused by OSA can antagonize the natural dipping phenomenon, meanwhile, the chronic HTN leading to endothelial dysfunction, vasculature abnormity, and insensitive baroreceptors may further inhibit the reflex dipping phenomenon (30).

In animal models as well as in humans, exposure to intermittent hypoxia and disruption of circadian rhythms have been shown to be associated with pancreatic beta cell loss and dysfunction, metabolic abnormalities, impaired function of the autonomic nervous system, renin-angiotensin system, and organ malfunction in the target organ (31, 32). Insulin resistance may in turn contribute to the development of non-dipper hypertension (33). The above superimposed changes may further aggravate metabolic abnormalities and associated cardiovascular events.

Previous studies paid more attention to SBP patterns than to DBP (34). In the present study, we explored the association of both systolic and diastolic BP patterns with new-onset diabetes and found that DBP non-dippers were significantly associated with higher risk of new-onset diabetes after adjustment for confounding factors, while SBP non-dippers were non-significant after full adjustment. Our findings are in agreement with several studies that have focused on the association of both SBP and DBP modes with OSA. A case-control study showed that patients with OSA had increased ambulatory DBP during both day and night and increased SBP during the night, compared to closely matched control subjects (35). A retrospective study found that subjects with more severe intermittent hypoxia and sleep fragmentation had significant higher SBP and DBP, and were more likely to have abnormal DBP than those with less severe intermittent hypoxia and sleep fragmentation (36). These findings

TABLE 2 Multivariate Cox regression analysis of association between circadian BP patterns and new-onset diabetes.

Variable	New-onset diabetes n (%)	Incidence rate per 1000 person-years	Crude Model		Model 1		Model 2		Model 3	
			HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
BP patterns (SBP and/or DBP)										
Dippers (n=759)	68 (9.0)	13.4	1 [reference]		1 [reference]		1 [reference]		1 [reference]	
Non-dippers (n=1082)	149 (13.8)	21.0	1.57 (1.18-2.09)	0.002	1.41 (1.05-1.89)	0.022	1.51 (1.12-2.03)	0.006	1.53 (1.14-2.06)	0.005
SBP patterns										
Dippers (n=540)	51 (9.4)	14.0	1 [reference]		1 [reference]		1 [reference]		1 [reference]	
Non-dippers (n=1301)	166 (12.8)	19.5	1.40 (1.02-1.92)	0.036	1.25 (0.91-1.72)	0.169	1.30 (0.95-1.80)	0.106	1.35 (0.98-1.86)	0.070
DBP patterns										
Dippers (n=613)	56 (9.1)	13.7	1 [reference]		1 [reference]		1 [reference]		1 [reference]	
Non-dippers (n=1228)	161 (13.1)	19.9	1.47 (1.09-2.00)	0.013	1.35 (0.99-1.84)	0.057	1.52 (1.11-2.08)	0.009	1.54 (1.12-2.10)	0.008

Crude model: Unadjusted. Model 1: adjusted for age, gender, drinking status, smoking status, BMI, office SBP, office DBP, hypertension duration, baseline prediabetes. Model 2: adjusted for all the variables in model 1, plus triglyceride, HDL-C, fasting blood glucose, mean daytime DBP, ACEI/ARBs use, CCBs use, statins use, AHI and nadir SaO_2. Model 3: based on minimal sufficient adjustment sets for estimating the total effect of non-dipping pattern on new-onset diabetes: age, gender, drinking status, hypertension duration, baseline prediabetes, BMI, fasting blood glucose, eGFR, serum potassium, serum sodium, mean daytime DBP, ACEI/ARBs use, AHI, nadir SaO_2, and regular CPAP treatment.
HR, hazard ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, blood pressure; HDL-C, high-density lipoprotein cholesterol; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; AHI, apnea hypopnea index; SaO_2, oxygen saturation; hs-CRP, high sensitivity C-reactive protein; eGRF, estimated glomerular filtration rate.

TABLE 3 Association between non-dipping pattern and new-onset diabetes stratified by subgroups.

Subgroup	N	New-onset diabetes, n (%)	Incidence rate per 1000 person-years	Full adjusted HR (95% CI)	*P*	*P* for interaction
Gender						0.532
Male	1273	144 (11.3)	17.0	1.65 (1.15-2.36)	0.007	
Female	568	73 (12.9)	19.8	1.40 (0.83-2.37)	0.208	
Age, years						0.170
≥60	286	40 (14.0)	21.9	1.27 (0.59-2.71)	0.545	
<60	1555	177 (11.4)	17.1	1.57 (1.13-2.17)	0.007	
BMI, kg/m^2						0.459
≥28	891	131 (14.7)	22.6	1.30 (0.89-1.91)	0.176	
<28	950	86 (9.1)	13.5	2.33 (1.42-3.83)	0.001	
Current Drinker						0.165
yes	644	67 (10.4)	15.4	1.90 (1.11-3.25)	0.019	
no	1197	150 (12.5)	19.2	1.40 (0.98-2.02)	0.065	
Hypertension duration						0.322
≥5 years	773	95 (12.3)	18.9	1.36 (0.86-2.14)	0.191	
<5 years	1068	122 (12.4)	17.1	1.81 (1.21-2.70)	0.004	

(Continued)

TABLE 3 Continued

Subgroup	N	New-onset diabetes, n (%)	Incidence rate per 1000 person-years	Full adjusted HR (95% CI)	*P*	*P* for interaction
AHI, events/hour						0.637
≥15	1116	153 (13.6)	20.9	1.72 (1.19-2.47)	0.004	
<15	725	65 (9.0)	13.4	1.21 (0.71-2.05)	0.490	
ACEI/ARBs use						0.677
yes	894	120 (13.4)	20.2	1.40 (0.95-2.07)	0.094	
no	947	97 (10.2)	15.6	1.78 (1.11-2.85)	0.017	
Statins use						0.817
yes	625	94 (15.0)	23.9	1.54 (0.98-2.41)	0.059	
no	1216	123 (10.1)	14.9	1.60 (1.06-2.41)	0.024	

full adjusted model: based on minimal sufficient adjustment sets for estimating the total effect of non-dipping pattern on new-onset diabetes: age, gender, drinking status, hypertension duration, baseline prediabetes, BMI, fasting blood glucose, eGFR, serum potassium, serum sodium, mean daytime DBP, ACEI/ARBs use, AHI, nadir SaO_2, and regular CPAP treatment.
BMI, body mass index; eGRF, estimated glomerular filtration rate; AHI, apnea hypopnea index; SaO_2, oxygen saturation; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker.

suggest that DBP mode is more likely to be specific in patients with OSA. A longitudinal analysis of the Wisconsin Sleep Cohort indicated that there was a dose-response greater risk of developing both SBP and DBP non-dipping patterns with greater severity of OSA in rapid eye movement (REM) sleep (37). Moreover, DBP non-dipping was significantly associated with the REM AHI, but not non-REM or total AHI (37), while SBP non-dipping was significantly associated with total AHI (30). It is well established that REM sleep is associated with greater sympathetic activity and cardiovascular instability in patients with OSA, which may explain why the risk of new onset diabetes subtly differs between SBP and DBP non-dipping patterns.

Elevated sleep-time BP has also been proposed as an important prognostic marker of diabetes. MAPEC study comprising 2,656 individuals without diabetes and with baseline BP ranging from normotension to HTN, during a 5.9-year follow-up, indicated that elevated sleep-time SBP is an independent prognostic marker for new-onset diabetes and lowering asleep BP could be a significant method for reducing new-onset diabetes risk. Moreover, those with new-onset diabetes were likely to have OSA at baseline (38). Nonetheless, neither mean nighttime SBP nor DBP was found to be associated with new-onset diabetes in the present study, the main reason for this may be attributed to the relatively high percentage of participants with elevated nighttime BP, 89.6% for the whole cohort, 95.4% for the non-dippers and 81.3% for the dippers, and 90.9% of the participants were on antihypertensive treatment. In the sensitivity analysis, the association between non-dippers and the risk of new-onset diabetes was unchanged in those excluding normal nighttime BP.

Currently, solid evidences of adverse prognosis of non-dipping pattern on cardiovascular risks and events provide justification for complete 24-h BP control as the primary goal of antihypertensive treatment. We therefore support the role of ABPM as an inexpensive, widely available screening and monitoring tool for the diagnosis of abnormal BP patterns in hypertensive patients with OSA, pursuing an optimized treatment and management of non-dipping BP for preventing diabetes.

CPAP is the current standard of treatment for OSA and seems to improve nocturnal BP dipping (39). Meta-analyses have shown a significant decrease in nighttime BP as well as a long-term (12 weeks) reduction in mean and diastolic BP with CPAP device usage of 4 or more hours per night (40, 41). A meta-analyses included six randomized controlled trials revealed that CPAP therapy has a favorable effect on insulin resistance in adult participants with OSA without diabetes (42). VAMONOS study demonstrated that only an outstanding compliance (defined as ≥90% of nights and 8 h/night) to CPAP reduced fasting blood glucose in patients with OSA. Longitudinally, higher levels of therapeutic adherence may affect the rate of incident impaired fasting glucose, prediabetes, and type 2 diabetes mellitus (T2DM), despite the observed weight gains (43). A recent meta-analysis included seven trials (enrolling 691 participants) determined that CPAP treatment significantly improved glycemic control and insulin resistance in patients with T2DM and contemporary OSA (44). However, CPAP therapy remained so far mixed results in improving glucose metabolism (45), herein, non-dipping BP pattern could be an important hallmark to determine high-risk patients and may need to be considered as an important clinical implication for early prevention of diabetes in hypertensive patients with OSA.

BP lowering has been an established strategy for the prevention of new-onset type 2 diabetes in hypertensive patients (46). To achieve 24-h BP control, evening or bedtime administration of antihypertensive drugs has been proposed as a potentially more effective strategy to control nocturnal hypertension, normalize the night-time BP dip. Previous study indicated that bedtime HTN treatment, in conjunction with proper patient evaluation by ABPM to corroborate the diagnosis of HTN and avoid treatment-induced nocturnal hypotension, should be the preferred therapeutic scheme for type 2 diabetes mellitus. However, it might be argued that bedtime dosing is a reasonable approach to be applied specifically to non-dippers, or patients with isolated night-time hypertension. To date, the supporting evidence, clinical relevance and indications for bedtime dosing remain debatable. The current evidence on the

comparative impact of bedtime versus other times of antihypertensive drug dosing on 24-h BP profile and on cardiovascular morbidity and mortality is limited by insufficient design and/or rigor of the available studies. The relevant ongoing trails and their results are expected to shed light on the impact of bedtime versus morning drug dosing on outcome (47). Treatment In Morning versus Evening (TIME) study has recently revealed that evening dosing of commonly used antihypertensive medications is no different from morning dosing in terms of major cardiovascular outcomes in hypertensive subjects (48). However, it remains unclear which treatment (e.g., CPAP, bedtime HTN therapy or combination) is optimal for preventing diabetes in patients with non-dipping HTN and OSA, further studies may need to focus on this population (47).

Our study has some limitations. First, current guidelines recommend the assessment of average daytime and nighttime BP values to be based on the individuals' sleeping times and the diagnosis of non-dippers to be confirmed with repeat ABPM. In this study, nighttime BP values were fixed from 23:00 to 08:00 and BP patterns were assessed only at the enrolment visit without repetition. Nonetheless, it was reported that the use of fixed-time periods may be a reasonable alternative approach for self-report in ABPM (49). Second, we failed to follow up ABPM so that the change of BP pattern was unclear, however, in a prospective study, of all dippers, only 42.7% remained dippers, while of all non-dippers, 81.4% remained non-dippers in the follow-up (22). Therefore, it is unlikely to overestimate the risk of non-dipping BP pattern for new-onset diabetes in this study. Third, only 2.7% patients received regular CPAP treatment possibly due to poor compliance or acceptance, thus we could not evaluate the effect of CPAP treatment on prevention for diabetes. In addition, we failed to record the administration time of antihypertensive drugs for each patient, nonetheless, bedtime dosing was not common in the routine prescription in our clinical practice. Fourth, this study is a retrospective cohort analysis and therefore is susceptible to residual confounding biases. Finally, UROSAH cohort is constituted by Chinese population from a single tertiary center, the results may not be extrapolated to other ethnicities, as previous studies reported that nocturnal dipping pattern differed by ethnicities (50).

Conclusions

We demonstrated that non-dippers are associated with approximately 1.5-fold higher risk for new-onset diabetes than dippers among hypertensive patients with OSA, suggesting that non-dipping BP pattern may need to be considered as an important clinical implication for early prevention of diabetes among this population.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the People's Hospital of Xinjiang Uygur Autonomous Region. The patients/participants provided their written informed consent to participate in this study.

Author contributions

QL was responsible for design, data collection, analysis and writing manuscript. NL was responsible for design, conduct, data collection and guiding the whole study. QZ, XY, MW, MH, XC, JH and LG participated in conduct/data collection and analysis. AA, LY, and XL participated in conduct/data collection. All authors contributed to the article and approved the submitted version.

Funding

This research was supported by Key Research and Development Project of Xinjiang Uygur Autonomous Region (2022B03009, 2022B03009-1).

Acknowledgments

We thank all participants and staff of the UROSAH study for their important contributions.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1083179/full#supplementary-material

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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 22 February 2023
DOI 10.3389/fendo.2023.1051592

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Clinical Diabetes, a section of the journal Frontiers in Endocrinology

RECEIVED 23 September 2022
ACCEPTED 06 February 2023
PUBLISHED 22 February 2023

CITATION
Miyamura K, Nawa N, Isumi A, Doi S, Ochi M and Fujiwara T (2023) Association between skipping breakfast and prediabetes among adolescence in Japan: Results from A-CHILD study. *Front. Endocrinol.* 14:1051592. doi: 10.3389/fendo.2023.1051592

Association between skipping breakfast and prediabetes among adolescence in Japan: Results from A-CHILD study

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Objective: Adolescents with prediabetes are at high risk of developing type 2 diabetes in later life. It is necessary to identify risk factors for prediabetes in adolescents. This study aimed to examine the association between skipping breakfast and prediabetes among adolescents in Japan.

Study design: We used the population-based cross-sectional data of eighth grade in junior high school students from the Adachi Child Health Impact of Living Difficulty (A-CHILD) study conducted in Adachi City, Tokyo, Japan, in 2016, 2018, and 2020. Skipping breakfast was assessed using self-reported questionnaires (N=1510). Prediabetes was defined as hemoglobin A1c (HbA1c) levels of 5.6-6.4%. The association between skipping breakfast and prediabetes was evaluated using multivariate logistic regression analysis. Stratified analysis was also performed using BMI, 1 SD or more, or less than 1SD, as overweight was defined as 1SD or more.

Results: Students who skipped breakfast were 16.4% (n=248). The prevalence of prediabetes was 3.8% (n=58). Skipping breakfast exhibited a significant association with prediabetes (OR:1.95, 95% CI: 1.03 to 3.69) after adjusting for sex, annual household income, family history of diabetes mellitus, BMI, and survey year. Stratified analysis showed stronger association among students with overweight (BMI ≥1SD) (OR=4.31, 95% CI 1.06-17.58), while non-sigificant among students without overweight (BMI<1SD) (OR=1.62, 95% CI 0.76-3.47).

Conclusions: Skipping breakfast in Japanese adolescents, especially those with overweight, was associated with prediabetes. The promotion of avoiding skipping breakfast may help to prevent prediabetes.

KEYWORDS

skipping breakfast, type 2 diabetes, prediabetes, adolescent, HbA1c

Introduction

Type 2 diabetes is an emerging and unsolved global health problem. Recent studies reported that the prevalence of type 2 diabetes in adults worldwide was about 8%, and the incidence of diabetes are plateauing (1–3). Type 2 diabetes can lead to blindness, dialysis, and cardiovascular disease, significantly impairing patients' quality of life (1). The prevalence of patients with young-onset type 2 diabetes is increasing worldwide (4, 5), and mortality and cardiovascular morbidity associated with type 2 diabetes differed significantly by age at diagnosis, with mortality and cardiovascular morbidity being highest among patients with early-diagnosed type 2 diabetes (6). To prevent type 2 diabetes, there is a need to identify risk factors in early-stage, including adolescents with prediabetes (7).

To identify possible risk factors for prediabetes in adolescence, the risk factors for type 2 diabetes would be the most prominent. For example, sedentary lifestyle or lack of physical exercise (8), improper dietary intakes (9), obesity, and family history of diabetes are well documented as risk factors for type 2 diabetes (8). Among them, we focus on skipping breakfast as a risk factor for prediabetes in adolescence because it is prevalent among adolescents, for example, 8.0% in junior high school in Japan (10, 11). Previous studies have suggested robust biological mechanisms in the association between skipping breakfast and prediabetes. Skipping breakfast could affect glucose metabolism by elevating free fatty acid level (12) and disrupting circadian rhythms (13). Furthermore, skipping breakfast can be associated with increased appetite (12) and poor diet (14). In addition, skipping breakfast may also decrease physical activity in the morning (15, 16).

A few cross-sectional studies showed that skipping breakfast was associated with elevated fasting glucose levels in childhood (aged 6-17 years old) (17, 18). However, population-based studies of adolescents in Asian populations are lacking. Considering the biological mechanisms of the effects of skipping breakfast on glucose metabolism, racial differences in insulin sensitivity and insulin response (19) may result in racial differences in the risk of skipping breakfast. In a European population-based study, significant differences among breakfast consumption habits and fasting blood glucose were seen only in boys (18). In a Brazilian study, a higher frequency of eating breakfast was negatively correlated with fasting blood glucose levels (17). However, it may be difficult to generalize the results because researchers investigated only children with obesity, with the subjects recruited *via* television commercials and newspaper advertisements. Conversely, a study among primary school children in Taiwan reported no association between skipping breakfast and prediabetes using fasting glucose levels (20). However, it may be too early to assess the associations because insulin resistance increases during adolescence (21).

The effect of skipping breakfast on glucose metabolism may be even higher in children with obesity because obesity increases insulin resistance and the risk of glucose intolerance (22). In individuals without obesity, skipping breakfast may decrease total daily energy intake. In contrast, in individuals with obesity, skipping breakfast may increase energy intake in the second half of the day without decreasing total energy intake (15, 16, 23). In other words, obesity may be an effect modifier in the association between skipping breakfast and diabetes risk. In addition, it has been reported that Asians are more likely to accumulate visceral fat even at the same BMI and to develop diabetes even with mild obesity compared to Whites (24). Therefore, it is also essential to evaluate the possibility that children with overweight may be a high-risk group.

In this research, we used a set of population-based data of junior high school children (aged 13–14 years old) from the Adachi Child Health Impact of Living Difficulty (A-CHILD) study in Tokyo, Japan, collected in 2016, 2018, and 2020. This study aimed to examine the association between skipping breakfast and prediabetes during adolescence in Japan and whether overweight status modify the association.

Methods

Study design and subjects

We used the cross-sectional data from the A-CHILD study conducted in Adachi City, Tokyo, Japan, in 2016, 2018, and 2020 (25–27). Details of this study protocol can be found somewhere (27). This study was approved by the Ethics Committee at the National Center for Child Health and Development (Study ID: 1147) and Tokyo Medical and Dental University (Study ID: M2016-284). Self-reported questionnaires with unique anonymous ID were administered to children in representative junior high schools (13-14 years old) in October 2016, 2018, and 2020. Children and their parents answered questionnaires at home and returned the questionnaires to their schools. Children responded to questions about lifestyle, while parents responded to questions about the family environment and their medical history. In 2016, 588 questionnaires were collected (77.9% return rate), in 2018, 583 questionnaires were collected (86.2% return rate), and in 2020, 551 questionnaires were collected (83.6% return rate), for a total of 1722 questionnaires collected (82.4% return rate). Questionnaire responses were linked to school health checkup data for body mass index (BMI) and blood test data conducted in Adachi City including HbA1c levels. Student participation in the health checkups was voluntary. The overall participation rate for health checkups was 75.4%, with 66.5% in 2016, 82.0% in 2018, and 79.0% in 2020.

Parents or children who did not respond, who left all answers blank, who did not agree to participate in the study, or whose children did not receive school checkups were excluded as invalid responses, and the remaining respondents were considered valid. Children who had missing data about the frequency of breakfast or HbA1c value were excluded. Children with anemia (defined as less than 12.0 g/dl of hemoglobin levels (28)) were also excluded because chronic anemia such as iron deficiency anemia elevates HbA1c level due to the effect of erythrocyte turnover although blood glucose does not elevate (29). The analysis was carried out using the data of 1510 participants (Figure 1).

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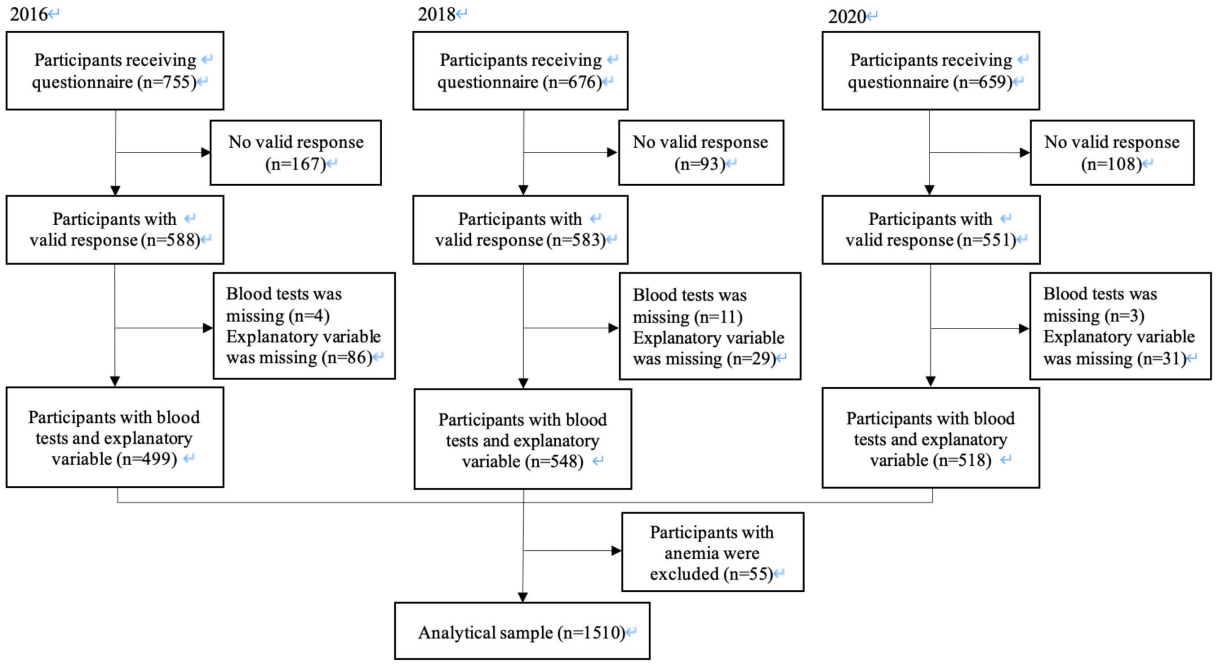

FIGURE 1
Participant flow chart. Of the 2090 2nd year students in seven representative junior high schools in Adachi City in 2016, 2018 and 2020, we analyzed 1510 students, who provided data for the frequency of breakfast and the blood tests.

Skipping breakfast

Skipping breakfast was assessed using the following question "How often do you eat breakfast per week?" based on previous studies (18, 20). The responses to this question were "every day," "sometimes," "rarely," or "never." To compare those who eat breakfast every day with those who do not eat breakfast every day, we collapsed four categories into two: "every day" or "sometimes/rarely/never".

Prediabetes

In this study, we evaluated HbA1c levels of 5.6-6.4% as prediabetes because the Japanese Diabetes Diagnostic Criteria Review Committee considers HbA1c levels of 5.6-6.4% as a group at high risk of developing diabetes in the future (30). We took a venipuncture blood sample from the arm at the laboratory and measured HbA1c level using an enzymatic assay. The students were not required to fast prior to having the blood test.

Covariates

Breakfast habits and risk of prediabetes are affected by demographic factors and socioeconomic status (8, 31). We chose child sex, annual household income as socioeconomic status, family history of diabetes, BMI, and survey year, as covariates, based on previous studies (17, 18, 20). Annual household income was categorized into four groups (<3.0 million yen, 3-6 million yen, 6-10 million yen, ≥10 million yen) based on the previous study (25). Family history of diabetes was categorized as "yes" when mother or father of participants had diabetes, and "no" when both mother and father of participants did not have diabetes. Children's BMI was calculated from their height and weight and assessed by z-scores based on the WHO Child Growth Standards according to age and sex, which can be applied to Japanese (32). BMI was categorized into three groups (<-1SD, -1SD to1SD, ≥1SD).

Items related to lifestyle habits other than breakfast habits were also investigated, such as sleep and exercise habits. Wake-up time was categorized into three groups (< 1 time/week, 1-2 times/week, ≥3 times/week). Sleep duration was calculated from the difference between waking and sleeping times for each hourly category because we did not ask about sleep duration. For example, the "7:00 - 8:00 a.m." wake-up time category was considered as 7:30, and the "after 24:00" bedtime category was considered as 24:30. If the person went to bed at 1:00, his/her sleep duration could have been overestimated. Sleep duration was categorized into four groups (≤ 6hours, 7hours, 8-10 hours, ≥11 hours) based on a consensus statement of the American Academy of Sleep Medicine (33). The frequency of exercise was categorized into three groups (< 1 time/week, 1-2 times/week, ≥3 times/week). Missing data with all covariates, which was adjusted for regression analysis, was created as a new dummy variable.

Statistical analysis

The association between skipping breakfast and prediabetes was evaluated using logistic regression analysis to calculate crude and

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adjusted odds ratio (OR) with 95% confidence intervals (CI). Sex, socioeconomic status, family history of diabetes, BMI, and survey year were put in the adjusted model. The VIF for the wake-up time variable was about 1 to 2, suggesting that there was no multicollinearity (34) (Supplementary Table 1). Thus, we performed the logistic regression analyses further adjusted for wake-up time and frequency of exercise. Furthermore, previous studies have shown that it is not the wake-up time but sleep duration (35, 36) and sleep disturbances (35) that affects diabetes. We also performed an analysis adjusted for sleeping time instead of wake-up time.

We also evaluated the effect of the interaction of overweight/obesity (BMI ≥ 1 SD (37)) on the association of skipping breakfast with prediabetes. Considering that estimating interactions requires a larger sample size than estimating main effects (38), the interaction term indicated a weak but possible effect modification (p-value for interaction 0.21), even though the interaction p-value is slightly larger (39). In other words, the effect of frequency of breakfast on prediabetes could vary depending on the presence or absence of overweight, we conducted stratified analysis by BMI ≥1 SD (i.e., students with overweight) and BMI <1 SD (i.e., students without overweight). Data analyses were carried out using STATA version 15 (Stata Corp LP, College Station, TX, USA).

Results

The proportion of students who ate breakfast every day and sometimes/rarely/never were 83.6% and 16.4%, respectively. The prevalence of prediabetes was 3.8%. There were no students whose HbA1c level was more than 6.5%, which is one of the diagnostic criteria of diabetes (American Diabetes Association 2010). There was no large change in the percentage of students who ate breakfast daily and in the prevalence of prediabetes between survey years. (Supplementary Table 2). The proportion of boys and girls were similar. A total of 12.3% had an annual household income of fewer than 3million yen. The percentage of girls who did not have breakfast every day (19%) was greater than that of boys who did not have breakfast every day (14%) (Table 1).

Table 2 shows the odds ratio (OR) of skipping breakfast for prediabetes. Students who did not eat breakfast every day were 1.66 times more likely to have prediabetes than those who ate breakfast

TABLE 1 Characteristics of participants (N=1510).

		Total	Frequency of breakfast	
			Every day	Sometimes/rarely/never
		(N=1510)	(N=1262; 83.6%)	(N=248; 16.4%)
		N (%)	N (%)	N (%)
Prediabetes	HbA1c<5.6	1452 (96.2%)	1218 (96.5%)	234 (94.4%)
	HbA1c≧5.6	58 (3.8%)	44 (3.5%)	14 (5.6%)
Child Sex	Boy	757 (50.1%)	651 (51.6%)	106 (42.7%)
	Girl	753 (49.9%)	611 (48.4%)	142 (57.3%)
	Missing	0 (0%)	0 (0%)	0 (0%)
Annual household income (million yen)	< 3	185 (12.3%)	141 (11.2%)	44 (17.7%)
	3 - 6	471 (31.2%)	400 (31.7%)	71 (28.6%)
	6 - 10	500 (33.1%)	434 (34.4%)	66 (26.6%)
	≥ 10	137 (9.1%)	122 (9.7%)	15 (6.0%)
	Unknown/Missing	217 (14.4%)	165 (13.1%)	52 (21.0%)
Family history of diabetes	No	1440 (95.4%)	1204 (95.4%)	236 (95.2%)
	Yes	70 (4.6%)	58 (4.6%)	12 (4.8%)
	Missing	0 (0%)	0 (0%)	0 (0%)
BMI	<-1SD	262 (17.4%)	227 (18.0%)	35 (14.1%)
	-1SD to 1SD	991 (65.6%)	833 (66.0%)	158 (63.7%)
	≥1SD	228 (15.1%)	178 (14.1%)	50 (20.2%)
	Missing	29 (1.9%)	24 (1.9%)	5 (2.0%)
Survey year	2016	483 (32.0%)	405 (32.1%)	78 (31.5%)
	2018	525 (34.8%)	435 (34.5%)	90 (36.3%)
	2020	502 (33.2%)	422 (33.4%)	80 (32.3%)

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TABLE 2 Odds ratio for prediabetes and skipping breakfast (n=1510).

		Crude		Adjusted model	
		OR	95%CI	OR	95%CI
Frequency of breakfast	Everyday	Ref		Ref	
	Sometimes/rarely/never	1.66	(0.89, 3.07)	**1.95**	**(1.03, 3.69)**
Child sex	Boy	Ref		Ref	
	Girl	0.56	(0.32, 0.96)	0.54	(0.31, 0.94)
Annual household income (million yen)	< 3	Ref		Ref	
	3 - 6	1.39	(0.45, 4.27)	1.45	(0.47, 4.48)
	6 - 10	2.99	(1.04, 8.59)	3.10	(1.07, 8.98)
	≥ 10	1.36	(0.33, 5.54)	1.42	(0.35, 5.83)
	Unknown/Missing	1.07	(0.28, 4.03)	1.09	(0.28, 4.14)
Family history of diabetes	No	Ref		Ref	
	Yes	1.56	(0.55, 4.42)	1.25	(0.43, 3.67)
BMI	<-1SD	0.87	(0.42, 1.82)	0.84	(0.40, 1.76)
	-1SD to 1SD	Ref		Ref	
	≥1SD	1.12	(0.55, 2.28)	1.00	(0.48, 2.09)
Year	2016	Ref		Ref	
	2018	1.02	(0.54, 1.92)	1.02	(0.54, 1.95)
	2020	0.91	(0.47, 1.75)	0.84	(0.43, 1.64)

OR, Odds ratio; CI, confidence interval.
Adjusted model: Adjusted for child sex, annual household income, family history of diabetes, BMI, and survey year.
Values in bold indicate statistically significant results.

every day in the crude model (OR: 1.66, 95% CI: 0.89 to 3.07). After adjusting for child sex, annual household income, family history of diabetes, skipping breakfast showed significant association with prediabetes (OR:1.95, 95% CI: 1.03 to 3.69) (Adjusted model). The OR of skipping breakfast to annual household income determined using univariate logistic regression was a negative association (OR: 0.39, 95% CI: 0.21 to 0.74 ("≥ 10 million yen" with reference to "<3million yen")), whereas that of prediabetes to annual household income determined using univariate logistic regression was a positive association (OR: 1.36, 95% CI: 0.33 to 5.5 ("≥ 10 million yen" with reference to "<3million yen")). Thus, annual household income was a negative confounder (40), leading to an underestimation of its effect. For this reason, the OR increased after adjusting for annual household income in the adjusted model.

Table 3 shows the odds ratio (OR) of skipping breakfast for prediabetes stratified by BMI. Among students with overweight (BMI≥1SD), skipping breakfast showed stronger association with prediabetes in the adjusted model (OR: 4.31, 95% CI: 1.06, 17.58). In contrast, among students without overweight (BMI<1SD), skipping breakfast was not statistically significantly associated with prediabetes in the adjusted model (OR: 1.62, 95% CI: 0.76, 3.47).

The proportion of those who skipped breakfast was higher among those who woke up late, slept longer on weekdays, and infrequently exercised (Supplementary Table 3). In univariate

TABLE 3 Odds ratio for prediabetes and skipping breakfast stratified by BMI .

	Frequency of breakfast	Crude		Adjusted model	
		OR	95%CI	OR	95%CI
BMI <1SD	Everyday	Ref		Ref	
	Sometimes/rarely/never	1.28	(0.61, 2.69)	1.62	(0.76, 3.47)
BMI ≥1SD	Everyday	Ref		Ref	
	Sometimes/rarely/never	**3.84**	**(1.07, 13.86)**	**4.31**	**(1.06, 17.58)**

OR, Odds ratio; CI, confidence interval.
Adjusted model: Adjusted for child sex, annual household income, family history of diabetes, BMI, and survey year.
Values in bold indicate statistically significant results.

analysis, breakfast skipping was significantly more frequent when waking up late, sleeping longer, and exercising less frequently (Supplementary Table 4). The logistic regression analysis with additional adjustments for wake-up time and exercise frequency, skipping breakfast remained significantly associated with prediabetes (OR: 2.01. 95%CI: 1.04, 3.89) (Supplementary Table 1). The logistic regression analysis adjusted for sleeping time instead of wake-up time showed similar results (OR: 1.98. 95%CI: 1.04, 3.79) (Supplementary Table 5).

Discussion

This study investigated the association between breakfast habits and prediabetes using HbA1c levels in Japanese adolescents. We found that skipping breakfast was associated with prediabetes in adolescents, and this association was stronger among students with overweight.

To our knowledge, this is the first study to investigate the association between skipping breakfast and prediabetes in adolescents in the Asian population. A few cross-sectional studies showed the association between skipping breakfast and fasting glucose levels on a continuous scale in childhood (17, 18). However, these studies did not examine the association with prediabetes using specified cutoff for blood glucose or HbA1c levels. Our results suggest that skipping breakfast is also associated with prediabetes as measured by HbA1c levels, in addition to being associated with elevated blood glucose levels. In addition, our results suggest that the effect of skipping breakfast on glucose metabolism was greater among students with overweight.

The various biological mechanisms explaining the association between skipping breakfast and prediabetes can be speculated. As fasting conditions prolonged, energy sources are supplied by not only gluconeogenesis and degradation of glycogen but also lipolysis, leading to elevated levels of free fatty acid (FFA) (41). For example, FFA levels before lunch in those who skip breakfast is higher than in those who consume breakfast (12). Since the elevated FFA levels affect glucose metabolism by disrupting insulin receptor signaling in skeletal muscle and liver, elevated FFA levels by skipping breakfast may play an important role in developing insulin resistance (42).

Another potential biological mechanism is the disruption of the circadian clock, which normally controls the activity of enzymes and hormones associated with glucose metabolism. The central circadian clock, which is located in the suprachiasmatic nucleus of the hypothalamus, mainly responds to the external light-dark cycle (43), and the peripheral clocks located in peripheral tissues such as β-cells, muscles, adipose tissues, and the liver mainly respond to meal timing and content (15, 44). Asynchrony of the central and the peripheral circadian clocks was associated with reducing insulin and glucagon-like peptide 1 (GLP-1) secretion (45), insulin resistance, β-cell proliferation, and β-cell apoptosis (44). Randomized controlled trials reported that skipping breakfast affects clock and clock-controlled gene expression (13), and those who skip breakfast exhibit greater glucose of area under the curve and glucose variability after lunch than healthy, lean adults who consume breakfast (13, 15). In addition, lower transcript levels of clock genes such as Bmal1, PER1, and PER3 were inversely correlated with HbA1c levels (46). In other words, the disruption of the circadian clock due to skipping breakfast may affect insulin secretion and other factors, causing an increase in postprandial blood glucose, leading to an increase in HbA1c, i.e., the risk of prediabetes.

Obesity persistently increases plasma FFA levels both in the basal state and after glucose loading, and is a major contributor to insulin resistance (47). Insulin resistance cause hyperinsulinemia to maintain normoglycemia. Hyperinsulinemia can maintain normal blood glucose levels to some degree; however, chronic progressive insulin resistance and compensatory insulin hypersecretion can be beta cell stress and eventually to beta-cell failure, leading to prediabetes and then to type 2 diabetes (48). When individuals with overweight skip breakfast, insulin resistance can be further increased. Blood glucose levels after lunch in individuals with overweight may be even higher than in individuals without overweight due to inadequate compensatory insulin secretion for the elevation of insulin resistance. Since the lower the HbA1c level, the higher the contribution of postprandial blood glucose to the HbA1c level than fasting blood glucose (49), prediabetes assessed by HbA1c levels may capture the effect of skipping breakfast on the postprandial glucose level.

Based on current findings, skipping breakfast can be a risk factor for impaired glucose metabolism, leading to prediabetes. Therefore, breakfast consumption might be effective in modulating insulin sensitivity and secretion and reducing the risk of prediabetes. Breakfast consumption may be recommended, especially for people with obesity. Breakfast intake could not affect weight gain (23). However, it is necessary to pay attention to eating habits other than breakfast so that eating breakfast does not lead to excessive daily caloric intake. Moreover, it is important to intervene targeting to parents at an earlier age to establish the habit of consuming breakfast daily because dietary patterns could be established between 1 and 2 years old and continue into young adulthood (50).

Several limitations of this study should be acknowledged. First, a self-reported questionnaire on skipping breakfast could result in recall bias. Moreover, individuals may have had different understandings of the options for breakfast frequency, as we did not provide specific explanations. However, since the breakfast categories were divided into “every day” and “sometimes/rarely/never,” there would be unlikely misclassifications. Second, breakfast was not defined by period since wake-up or a time frame in the morning. However, breakfast time on weekdays among junior high school students would not be very different. Third, we were unable to include blood glucose levels to diagnose prediabetes. Fourth, we were unable to assess the pubertal stage like the tanner stage of each student, although the effects of glucose metabolism may vary by tanner stage (51). Fifth, we were not able to exclude other specific types of diabetes, such as type 1 diabetes. However, there were no students whose HbA1c level was more than 6.5%, and the incidence of childhood-onset type 1 diabetes in Japan is low (2.25/100,000 persons) (52) compared with most European countries and the US. Sixth, given the somewhat large interaction p-value, studies with a larger sample size would be needed to confirm our findings. Finally,

this study is a cross-sectional study and does not clarify the causation between skipping breakfast and prediabetes in adolescents. In the future, longer duration randomized controlled trials and longitudinal studies from preschool children to adolescents are needed. In addition, it is necessary to evaluate the impact of skipping breakfast on prediabetes in other races to generalize our findings because there are racial differences in insulin sensitivity and insulin response (19). Analysis using indices of insulin sensitivity and insulin resistance calculated by fasting blood glucose and fasting insulin levels would also be helpful.

In summary, we found that skipping breakfast was associated with prediabetes after adjusting for the students' demographic, lifestyle, and socioeconomic status, and this association was stronger among students with overweight. Our findings suggest that avoiding skipping breakfast may help to prevent prediabetes, especially for people with overweight.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee at the National Center for Child Health and Development (Study ID: 1147) and Tokyo Medical and Dental University (Study ID: M2016-284). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

TF conceived the study. TF, MO, AI and SD conducted the survey and collected data. KM was primarily responsible for data analysis and wrote the first draft of paper. NN and TF reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by a Health Labour Sciences Research Grant, Comprehensive Research on Lifestyle Disease from the Japanese Ministry of Health, Labour and Welfare (H27-Jyunkankito-ippan-002), Research of Policy Planning and Evaluation from the Japanese Ministry of Health, Labour and Welfare (H29-Seisaku-Shitei-004), Innovative Research Program on Suicide Countermeasures (IRPSC), and Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (JSPS KAKENHI Grant Number 16H03276, 16K21669, 17J05974, 17K13245, 19K19310, 19K14029, 19K19309, 19K20109, 19K14172, 19J01614, 19H04879, 20K13945, and 21H04848), St. Luke's Life Science Institute Grants, the Japan Health Foundation Grants, and Research-Aid (Designated Theme), Meiji Yasuda Life Foundation of Health and Welfare.

Acknowledgments

We are particularly grateful to the staff members and central office of Adachi City Hall for conducting the survey. We would like to thank everyone who participated in the surveys. In particular, we would also like to thank Mayor Yayoi Kondo, Mr. Syuichiro Akiu, and Ms. Yuko Baba of Adachi City Hall, all of whom contributed significantly to completion of this study. TK. 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.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1051592/full#supplementary-material

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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 22 March 2023
DOI 10.3389/fendo.2023.1122164

OPEN ACCESS

EDITED BY
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SPECIALTY SECTION
This article was submitted to Clinical Diabetes, a section of the journal Frontiers in Endocrinology

RECEIVED 12 December 2022
ACCEPTED 02 March 2023
PUBLISHED 22 March 2023

CITATION
Santos KBM, Reis RCP, Duncan BB, D'Avila OP and Schmidt MI (2023) Access to diabetes diagnosis in Brazil based on recent testing and consultation: The Brazilian national health survey, 2013 and 2019.
Front. Endocrinol. 14:1122164.
doi: 10.3389/fendo.2023.1122164

Access to diabetes diagnosis in Brazil based on recent testing and consultation: The Brazilian national health survey, 2013 and 2019

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Background: Screening for undiagnosed diabetes using glucose testing is recommended globally to allow preventive action among those detected. Our aim was to evaluate the access to glucose testing to screen for diabetes in Brazil using self-reported information on recent testing and medical consultation from national surveys of Brazilian adults.

Methods: The *Pesquisa Nacional de Saúde* (PNS) was conducted in 2013 and 2019 drawing probabilistic samples of Brazilians aged 18 years and above. To evaluate glucose testing among those undiagnosed, we excluded those self-reporting a previous diagnosis of diabetes. We then defined recent access to diabetes diagnosis by considering the previous two years and choosing the last blood glucose test and the proximal medical consultation reported. We used Poisson regression with robust variance to assess correlates of access, expressing them with adjusted prevalence ratios (PR) and their 95% confidence intervals.

Results: Access to recent glucose testing documented that over 70% reported a recent glycemic test, 71% in 2013, and 77% in 2019. These findings are consistent with a wide recent access to medical consultation, 86% and 89% in 2013 and 2019, respectively. Reporting recent glucose testing and medical consultation may better reflect the actual access to medical diagnostic testing. When analyzing this joint outcome, diagnostic access was still wide, 67% and 74%, respectively. Greater access ($p< 0.001$) was seen for women (PR=1.16; 1.15-1.17), older individuals (PR=1.25; 1.22-1.28), and those with higher education (PR=1.17; 1.15-1.18), obesity (PR=1.06; 1.05-1.08), and hypertension (PR=1.12; 1.11-1.13). In contrast, lower access ($p<0.001$) was seen for those declaring being Black (PR=0.97; 0.95-0.99) or of mixed-race (PR=0.97; 0.96-0.98), those residing in rural areas (PR=0.89; 0.87-0.90), and not having a private health insurance plan (PR=0.85; 0.84-0.86).

Conclusions: Although access to diagnostic testing for diabetes is high in Brazil, partly due to its universal health system, social inequities are still present, demanding specific actions, particularly in rural areas and among those self-declaring as being Black or mixed-race.

KEYWORDS

diabetes mellitus, diagnosis, health care, health inequities, cross-sectional studies

1 Introduction

Diabetes is a chronic disease with a global impact. By 2021, 537 million people worldwide had diabetes. The growth in cases is skyrocketing, with an estimated 783 million people having diabetes by 2045. The projected increase in cases appears to be due to projected population aging and growth, urbanization, lifestyle, and environmental pollution, among other factors (1). Diabetes also is responsible for a great burden, placing diabetes among the principal causes of loss of health. For instance, in 2019, in the Americas, it was estimated that 409,000 adults aged 20 years or older died from diabetes (5-9% of all deaths). Diabetes was responsible for 2266 crude disability-adjusted life-year (DALYs) per 100,000 adults in the Americas (2). Owing to the frequently long period between the onset of the disease and the onset of diabetes symptoms, a considerable proportion of type 2 diabetes cases remain undiagnosed, leading to increased mortality, diabetes-related complications, and costs (1). Behavioral risk factors such as low physical activity and unhealthy diets are the main determinants of diabetes and its complications (3–5).

Not having consulted a doctor in the last year is one of the main determinants of the delayed diagnosis of mild and asymptomatic cases of diabetes (6). Therefore, the American Diabetes Association (ADA) recommends tracking diabetes in all individuals over the age of 35 or at any age for overweight/obese adults who have at least one additional risk factor for diabetes. Screening can be done directly by asking for a glycemic test for all, or in two steps, by applying the glycemic test only to those at higher risk by questionnaire. The ADA also recommends repeating the test every three years or more often for those at high risk (7). The Brazilian Society of Diabetes follows similar criteria, except for the age of screening, using a threshold of 45, instead of 35 years old (5).

In order to effectively act in the health-to-disease course, adequate access to health services is essential (8). Access is usually defined by the timely use of health services to achieve the best possible health outcomes (9). On the premise that health is a right of all citizens, ensuring universal access to cost-effective health services is mandatory and thus requires regular evaluation. To our knowledge, assessment of access to diabetes diagnosis has been assessed using nationwide representative samples in the United States and Puerto Rico, Argentina, and Sub-Saharan countries, with rates ranging from 77% to 22% (in decreasing order) (10–12).

To gain insight into the population coverage of glucose testing for the diagnosis of diabetes, our objective is to evaluate the access to glucose testing and medical consultation in Brazil in 2013 and 2019 using self-reported information on recent testing and medical consultation available in the *Pesquisa Nacional de Saúde* (PNS), a household national representative survey of Brazilian adults. In addition, we aimed to relate access to demographic, socioeconomic, and clinical factors.

2 Methods

2.1 The PNS surveys

The PNS is a national population-based household survey conducted by the Brazilian Institute of Geography and Statistics (IBGE) in partnership with the Ministry of Health, which has been conducted twice, in 2013 and 2019. The selection of participants was based on cluster probability sampling in three stages of selection and stratification of the primary sampling units (PSUs). The PSUs are formed by census tracts or composition of census tracts; the second stage units being households, selected to produce a fixed number of permanent private households for each PSU; the third stage units are residents aged 18 years or older (2013) and 15 years or older (2019), selected from a list of residents built at the time of the interview. For each one of the three stages, a simple random sampling was performed for the selection of the units. More information about the design of the surveys can be found elsewhere (13, 14).

Because of its complex sample design, and to estimate population parameters, the expansion factors or basic sample weights for the households, all residents, and the selected resident were provided for the PNS Surveys by IBGE. The basic weights were adjusted to correct for non-response, and calibrated according to Brazilian population projections by gender and age group (14, 15). In order to dimension the sample size with the desired level of precision for the 2019 PNS estimates, the IBGE considered some indicators of the 2013 edition of the PNS, such as data on non-communicable chronic diseases (NCDs) (diabetes, hypertension, depression), violence, use of health services, possession of health insurance, smoking, physical activity practice, and alcohol consumption, among others (14). The microdata files are available from the PNS website (16). For this study, we used data for adults 18 years or older.

2.2 Analytic sample

Figure 1 shows the sample flowchart of the Brazilian National Health Surveys conducted in 2013 and 2019. In 2013, of the 81,167

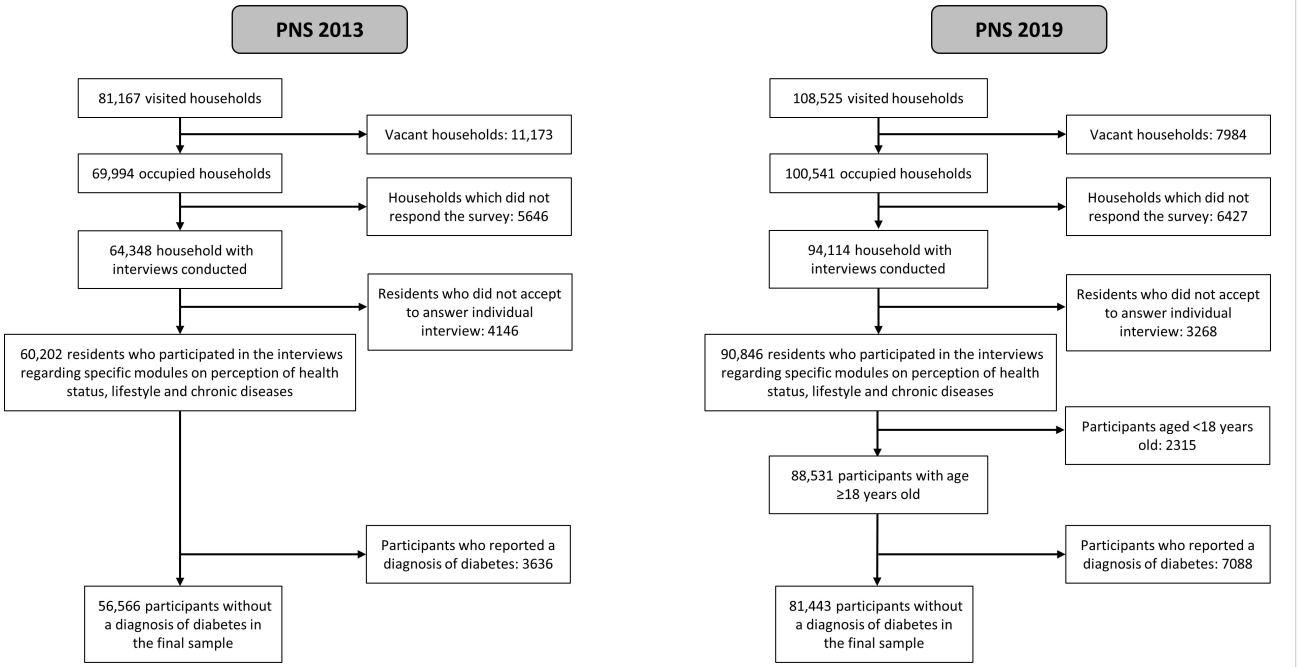

FIGURE 1
Flowchart of study participants, Brazilian National Health Survey, 2013 and 2019.

households selected, 11,173 were empty, 5646 did not answer the survey and 4146 individuals did not agree to answer the individual questionnaire, leaving 60,202 residents aged 18 years or older who answered the individual questionnaire. This corresponds to a response rate of 86% of total non-empty selected households. Of these, 3636 (6.03%) reported having diabetes, and 56,566 not having this diagnosis. In 2019, of the 108,525 households selected, 7984 were empty, 6427 did not answer the survey, and 3268 did not agree to answer the individual questionnaire, leaving 90,846 residents aged 15 years or older as respondents (~90% of total non-empty selected households). For this study we included respondents aged 18 years or older, which corresponded to 88,531 residents; of these, 7088 (6.53%) people reported having a diagnosis of diabetes, and 81,443 not having.

2.3 Measurements

The PNS questionnaire was divided into 20 modules in 2013, and 26 modules in 2019, and included characteristics of the households, all residents, and the selected resident. We used the following questions to analyze aspects describing access to glucose testing and medical consultation for those not reporting a previous diagnosis of diabetes. "When was the last time that you had a blood test to measure blood glucose, that is, blood sugar?" (Questions Q29 and Q29a, in 2013 and 2019, respectively); and "When was the last time that you consulted with a doctor?" (Questions J11 and J11a, in 2013 and 2019, respectively). For the last blood glucose test, the response options were as follows: less than 6 months, between 6 months and 1 year, between 1 and 2 years, between 2 and 3 years, 3 years or more, and never performed. For the medical consultation, the answer options were as follows: in the last 12 months, between 1 and 2 years, between 2 and 3 years, 3 years or more, and never performed.

We defined access to glucose testing (yes or no) for the detection of diabetes among those not previously diagnosed by a report of a glucose test within two years of the interview. Since screening for diabetes is recommended to occur every 1-3 years, we judged that a two-year period could be recent enough to characterize adequate screening. To evaluate the robustness of this glucose testing assessment to define access to medical diagnosis we also evaluated the joint occurrence of a recent glucose testing and a recent medical consultation.

In the 2013 edition, weight and height were measured, while in 2019, these variables were self-reported. Demographic, socioeconomic, and clinical factors were also obtained from the PNS questionnaires. Sociodemographic characteristics - sex: male and female; age group in years: 18-24, 25-39, 40-59, and 60 or greater (≥60); race/color: white, black, brown (mixed-race), Asian (yellow), and indigenous; education: with no formal education or incomplete elementary school (incomplete elementary), complete elementary school or incomplete high school (complete elementary), complete high school or incomplete higher education (complete high school), and complete higher education; geographic macro-region: Central-West, Northeast, North, Southeast, and South; type of census situation: urban and rural; having private health insurance: yes and no. Clinical factors - body mass index (BMI), calculated as weight in kilograms divided by height in meters squared: Low Weight/Normal (< 25 kg/m^2), Overweight (between 25 and 29.9 kg/m^2), and Obesity

(≥ 30 kg/m^2); the presence of hypertension: yes and no; diagnosed diabetes: yes and no.

2.4 Statistical analyses

To compare the results of the 2013 and 2019 PNS surveys, the IBGE recalibrated the PNS 2013 sample weights, based on the revised Brazilian population projection by gender and age used for the 2019 survey (17). The data of the two PNS editions were combined, using the survey year as a covariate, and making adjustments in the sample weights as suggested by Korn and Graubard (1999) (18), similar to those adopted in other studies (19, 20).

Sociodemographic and clinical characteristics were described by simple frequencies and percentages weighted by calibrated weights, provided together with the datasets by IBGE. The distribution of access variables to diagnostic services was described by weighted percentage and 95% confidence interval (95% CI). Comparisons of sociodemographic and clinical characteristics between the two editions of the PNS survey were evaluated using a chi-square test with the Rao-Scott adjustment (21).

The associations of access outcomes with sociodemographic and clinical characteristics were evaluated using adjusted prevalence ratios (PR) and 95% CI, estimated by Poisson regression models with robust variance. We built progressively larger models by adding factors likely to be related to access in the following order: gender, age, race/color, education, geographic macro-region, type of census situation, having private health insurance, and clinical conditions such as levels of BMI and hypertension. We checked for possible collinearity across the independent variables using the generalized variance inflation factor (GVIF) (22). We considered a threshold of 2.5 (VIF >2.5) as indicative of the need for further evaluation (23).

Data analysis was performed in the statistical software R (24), version 4.0.4 with the survey package (25) to take into account the complex sample design.

3 Results

We found a slight predominance of women; most were between ages 25 to 59 and declared to be White or mixed-race (Table 1). Few had completed higher education (13% and 16.4% in 2013 and 2019, respectively). Between 2013 and 2019 we observed an increased frequency of people with age 60 years old or over and with completed high school. We also noticed a slight increase in overweight and obesity, as well as a slight increase in a self-reported diagnosis of hypertension between surveys. About a third of the population had private health insurance in both survey years.

The descriptive data presented in Table 2 show ample access to blood glucose testing over the two years prior to the interview (2013 and 2019) among those not reporting a previous diabetes diagnosis, with a slight increase in the last survey (71.1% to 77.2%). The percentage of those who reported never having done a glucose test was small in 2013 (12.3%) and decreased to 6.8% in 2019. These data are consistent with a broad report of medical consultation in the 2 years before the study (85.6% and 89.2%, respectively). The percentage of that who reported never having had a medical consultation was minimal (0.8% and 0.6%, respectively).

To complement our assessment of the access to glucose testing as a mean of screening for diabetes we considered the joint occurrence of a recent glucose test and a recent medical consultation. Although frequencies were lower than when assessing only the frequency of glucose testing, they remained high (67% and 74%, each year, respectively).

Figure 2 illustrates the wide access to diabetes diagnosis for three measurements of access: (A) Last glucose test <2 years; (B) Last glucose test <2 years and Last consultation <2 years; (C) Last consultation <2 years, according to various characteristics. Access was generally higher in women, those aged 60 years or older, those with higher education, living in urban areas, and having private health insurance.

As illustrated in Figure 3, and described in detail in Supplementary Table 1, access to a recent glucose test was relatively higher in 2019 (PR=1.07; 1.06-1.08), consistent with the increase in recent consultation (PR=1.04; 1.03-1.04). Access to a recent glucose test was higher in women (PR=1.16; 1.15-1.17), those 60 years or older (PR=1.25; 1.22-1.28), with complete higher education (PR=1.17; 1.15-1.18), obesity (PR=1.06; 1.05-1.08) and a previous diagnosis of hypertension (PR=1.12; 1.11-1.13). Access to a recent glucose test was lower in people of Black (PR=0.97; 0.95-0.99) or mixed-race (PR=0.97; 0.96-0.98), living in rural areas (PR=0.89; 0.87-0.90) and without private health insurance (PR=0.85; 0.84-0.86). The report of a recent medical consultation showed a similar pattern of association.

When the recency of glucose testing was considered together with a reporting of a recent consultation, the associations showed a similar pattern. Access to a recent blood glucose test was relatively higher in 2019 (PR=1.09; 1.07-1.10), women (PR=1.21; 1.20-1.23), people 60 years of age or over (PR=1.25; 1.22-1.29), with a complete higher education (PR=1.16; 1.14-1.18), with obesity (PR=1.06; 1.05-1.08) and with diagnosed hypertension (PR=1.17; 1.16-1.19). It was relatively lower in people of yellow (Asian) race/color (PR=0.93; 0.88-0.99), living in rural areas (PR=0.89; 0.87-0.91), without a private health insurance plan (PR=0.81; 0.80-0.83) and living in the North region (PR=0.95; 0.93-0.98).

4 Discussion

Our findings from the PNS 2013 and 2019 show generally wide access to screening and diagnosis of diabetes in Brazil. Access is greater in women, the elderly, those living in the Southeast region, and those with overweight, obesity, and hypertension. These findings reflect the wide access to medical consultation in the two years before the interview. However, inequities in access related to low education, self-declaring as being Black, and living in rural areas and the North region warrant further attention.

The Unified Health System (*Sistema Único de Saúde* – SUS), implemented after the new constitution of 1988 in Brazil, provides universal access to all levels of health care, with a broad coverage of primary health care, the preferred gateway to health care in SUS.

TABLE 1 Sociodemographic and clinical characteristics of participants, without diabetes diagnosis [n (weighted %)], in the Brazilian National Health Survey, 2013 and 2019 (n = 138,009).

Characteristics	2013 n (%)	2019 n (%)	*p*-value†
Overall	n = 56,566	n = 81,443	-
Sex			0.549
Male	24,639 (47.6)	38,784 (47.3)	
Female	31,927 (52.4)	42,659 (52.7)	
Age (years)			<0.001
18-24	7789 (16.9)	8090 (14.9)	
25-39	20,486 (33.5)	25,072 (31.2)	
40-59	19,010 (33.9)	29,827 (35.2)	
≥60	9281 (15.8)	18,454 (18.7)	
Race/Color*			<0.001
White	22,550 (47.3)	29,675 (43.1)	
Black	5216 (9.0)	9253 (11.5)	
Mixed-race	27,904 (42.3)	41,292 (44.0)	
Yellow	504 (0.9)	597 (0.9)	
Indigenous	390 (0.4)	617 (0.5)	
Education			<0.001
Incomplete elementary	21,858 (37.6)	31,323 (32.8)	
Complete elementary	8774 (15.7)	11,226 (14.7)	
Complete high school	18,511 (33.8)	25,987 (36.1)	
Complete higher education	7423 (13.0)	12,907 (16.4)	
Region			0.321
Central-West	7027 (7.4)	9353 (7.6)	
Northeast	17,236 (26.7)	28,286 (26.6)	
North	11,998 (7.6)	15,895 (8.0)	
Southeast	13,244 (43.5)	17,603 (43.1)	
South	7061 (14.8)	10,306 (14.7)	
Census situation			0.958
Urban	46,152 (86.0)	62,484 (86.0)	
Rural	10,414 (14.0)	18,959 (14.0)	
Private health insurance			0.607
Yes	15,287 (30.0)	20,510 (29.7)	
No	41,279 (70.0)	60,933 (70.3)	
Body mass index*			0.209
Low Weight/Normal (< 25 kg/m^2)	24,510 (44.3)	34,842 (43.3)	
Overweight (between 25 and 29.9 kg/m^2)	20,215 (36.0)	29,965 (36.5)	
Obesity (≥ 30 kg/m^2)	11,049 (19.7)	15,795 (20.1)	
Hypertension			<0.001

(Continued)

TABLE 1 Continued

Characteristics	2013 n (%)	2019 n (%)	*p*-value†
Overall	n = 56,566	n = 81,443	-
Yes	10,252 (18.6)	17,959 (20.6)	
No	46,314 (81.4)	63,484 (79.4)	

*n slightly smaller due to missing values: Race/Color ($n_{missing}$ = 11); Body mass index ($n_{missing}$ = 1633).
†Rao-Scott chi-square test.

Between 2013 and 2019, coverage increased by 6.5 percentage points, from 56.1% to 62.6%, which corresponds to a proportional increase of 11.6%, with the inclusion of an additional 18.7 million residents in the Family Health Strategy (26). This may explain the ample access to medical consultation reported and the consequent large access to glucose testing described here.

For comparison, another Brazilian survey, Vigitel, conducted in state capitals in 2011 found a similar rate of recent glucose testing (76%). Factors related to higher testing were also similar (27). Of note, however, Vigitel data refer to those living in capital cities and thus its finding reflects more our specific results for urban areas (in 2013, 73.6%).

In the United States, a similarly high rate of recent (3 years) glucose testing was reported, 63.8% (11). In Argentina, as well, high rates were found (65.2% in 2009) (10). In sub-Saharan Africa, a pooled data analysis derived from nationwide samples found lower testing rates (only 22% of those overweight or obese had ever had glucose testing), being higher in countries with higher per capita income (12). Screening for undiagnosed diabetes based on glucose testing inevitably also detects prediabetes and this latter diagnosis may lead to overdiagnosis as well as unnecessary medical interventions (28, 29). A study developed in India revealed that HbA1C levels increase with age and points to the need to define age-specific cutoff points to avoid the risk of overdiagnosis and unnecessary initiation of treatment (30).

TABLE 2 Weighted percentage (95% CI) of adults without diabetes diagnosis, according to the time since the last medical consultation and last blood glucose test, in the Brazilian National Health Survey, 2013 and 2019 (n = 138,009).

Survey question	2013 % (95% CI)	2019 % (95% CI)	*p*-value†
Overall	n = 56,566	n = 81,443	-
When was the last time you had a blood test to measure your blood glucose?			<0.001
Less than 2 years	**71.1 (70.3, 71.9)**	**77.2 (76.6, 77.7)**	
2 years or more	16.6 (16.0, 17.1)	16.1 (15.6, 16.5)	
Never did	12.3 (11.8, 12.9)	6.8 (6.4, 7.1)	
When was the last time you saw a doctor?			<0.001
Less than 2 years	**85.6 (85.1, 86.2)**	**89.2 (88.8, 89.6)**	
2 years or more	13.6 (13.0, 14.1)	10.2 (9.8, 10.6)	
Never had been with a doctor	0.8 (0.6, 0.9)	0.6 (0.5, 0.7)	
Most recent consultation/blood glucose test			<0.001
< 2 years/< 2 years	**66.8 (66.0, 67.6)**	**73.8 (73.1, 74.4)**	
2 years or more/< 2 years	4.1 (3.9, 4.4)	3.3 (3.0, 3.5)	
Never been to doctor/< 2 years	0.2 (0.1, 0.2)	0.2 (0.1, 0.2)	
< 2 years/2 years or more	10.6 (10.1, 11.0)	10.8 (10.4, 11.2)	
2 years or older/2 years or more	5.8 (5.5, 6.2)	5.1 (4.8, 5.4)	
Never been to doctor/2 years or more	0.2 (0.1, 0.2)	0.2 (0.1, 0.2)	
< 2 years/Never did	8.3 (7.8, 8.7)	4.6 (4.4, 4.9)	
2 years or more/Never did	3.6 (3.3, 3.9)	1.8 (1.7, 2.0)	
Never been to the doctor/Never did	0.4 (0.3, 0.5)	0.3 (0.3, 0.4)	

†Rao-Scott chi-square test. The prevalence of outcomes (i.e., Recent blood glucose test, Recent medical consultation, and Recent glucose and consultation) are highlighted in bold.

FIGURE 2
Frequency of recent (over the previous 2 years) access to a diagnosis of diabetes by sociodemographic and clinical characteristics considering three options to define access: **(A)** Glucose test, **(B)** Glucose and medical consultation, **(C)** Medical consultation, Brazilian National Health Survey, 2013 and 2019. BMI, Body mass index; HTN, Hypertension.

That greater access to diagnosis occurred in women, older people, and those with higher education is consistent with data from other studies (31–33). Perception of health needs has been shown to be an important indicator of access and use of health services (31, 34, 35) and may explain our findings. Women may have a greater perception of the importance of medical care, greater utilization of health services for monitoring prenatal care and the follow-up of children (31, 36, 37), and perhaps greater motivation to do check-ups and participate in health promotion and disease prevention activities. Those in a higher age group are likely to have another diagnosis of chronic disease demanding longitudinal care thus facilitating opportunistic testing. In contrast, younger people do not perceive themselves as at risk of developing some disease and seek fewer health services, and also have fewer symptomatic illnesses leading to consults. The expansion of the public network in Brazil occurred mainly for primary health care (PHC), expanding access to medical consultations for a substantial portion of the Brazilian population (38, 39). However, differences remain in the use of services that benefit those who have health insurance. Although our data show greater access to diagnosis in those with private health insurance, the difference between these two groups has been decreasing. In 1998, people with private health insurance plans were 200% more likely to use a health service when they perceived a need for it than people without health insurance, but this difference was reduced to 70% in 2008 (38). The new funding model of PHC, implemented in 2019, through weighted capitation and payment for performance, induces a more adequate identification of people linked to each family health team and imposes the improvement of indicators seeking better results in care, which allows us to envision the expansion of access in PHC

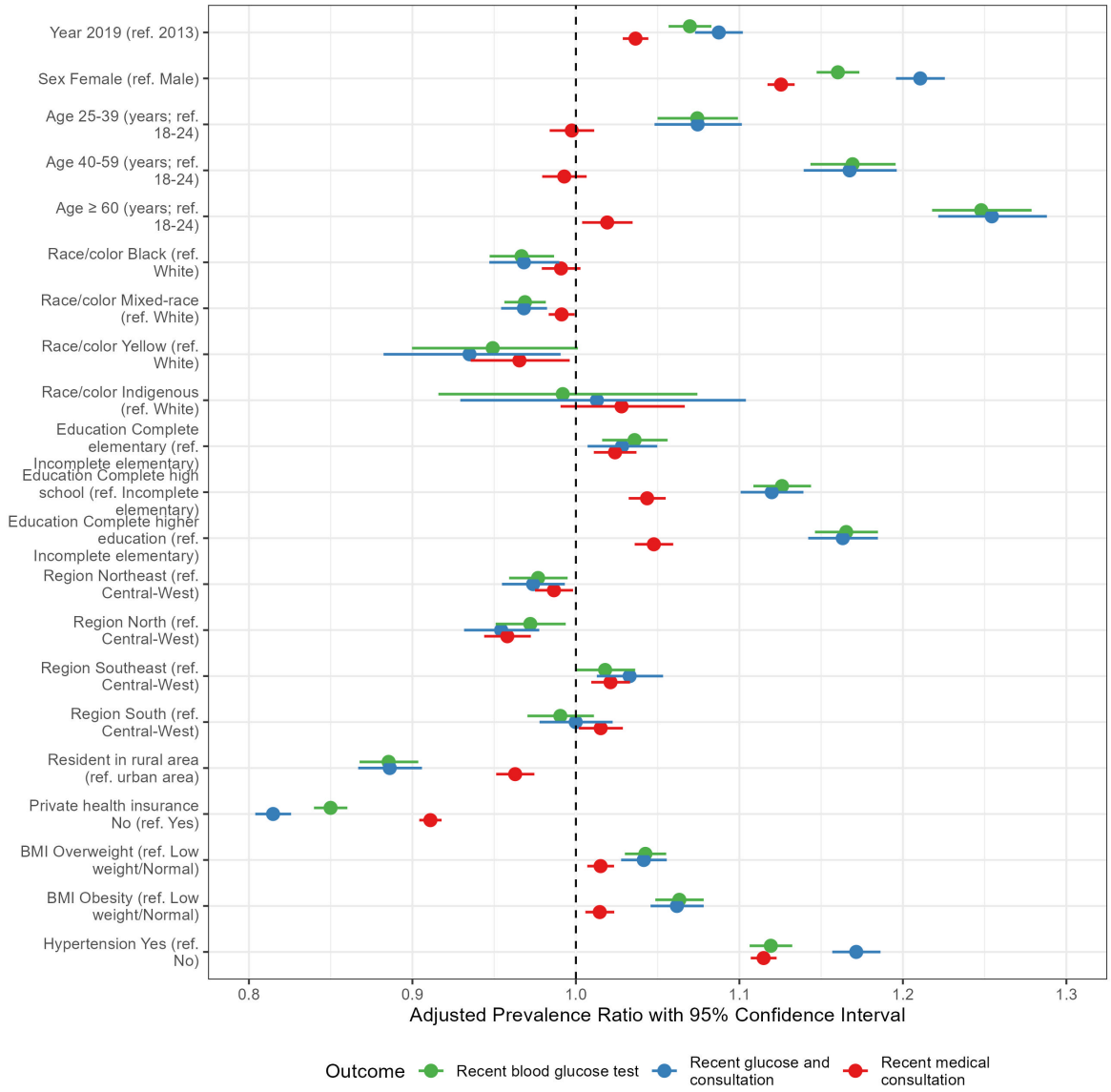

FIGURE 3
Association of survey year and sociodemographic and clinical characteristics with access to a recent glucose test, a recent medical consultation, or both, adjusted for gender, age, education, race/color, geographic macro-region, living in an urban or rural area, having private health insurance, and the year of the survey, as well as BMI and hypertension; the dashed vertical line represents PR = 1.0, meaning no association; PR values on the right side of the dashed line mean factors increasing the prevalence of recent access; otherwise, PR values on the left side of the dashed line mean factors associated with a lower prevalence of recent access. Brazilian National Health Survey, 2013 and 2019. BMI, Body mass index.

(40). The population with health insurance plans may also have a greater opportunity to access services because many use both SUS and supplementary health services (31, 41).

Although the findings demonstrate broad diagnostic access in the country, some gaps observed deserve discussion. First, a percentage of people without a previous diagnosis of diabetes reported not having had a recent blood glucose test (<2 years), even though they had a recent medical consultation (<2 years), 14.5% in 2013 and 12% in 2019, with a proportional reduction of 17% in the period. Although this may represent a loss of diagnostic opportunity, periodic blood glucose application every 1-3 years, recommended in guidelines (7), can mitigate this gap. The SUS has been expanding access to health care (38), and the increase in the frequency of consultations is associated with increased diagnosis (42–45), which explains, at least in part, the reduction of diagnostic loss in the period. Second, our data also show gaps in access to diabetes diagnosis, especially sociodemographic factors, such as those living in rural areas, declaring themselves Black or mixed-race, or having low education. These inequities can be attributed in part to differences in behaviour when seeking health care. Groups with lower income and/or lower education may delay the decision to seek health care due to negative experiences obtaining care in the past or related to the care they received, or due to other factors, such as the impossibility of missing work or the perception of no need for health counselling (38). Often also, other priorities in their lives may take on greater importance. Interventions focusing on risk factors,

added to actions in social determinants are necessary to expand access to diabetes diagnosis.

Our study has potential limitations. The first one refers to the cross-sectional design of the PNS survey that includes different participants in each sample, limiting the inferences of the associations that we report to the changes that occurred in the individuals studied. Second, data collection was based on self-reported information, and thus subject to information bias including recall bias. Although BMI calculations for the 2013 survey were based on measured weight and height, in 2019 they were based on self-report. Thus, misclassification may affect the associations here reported between the two years. Of note, however, a high agreement between self-reported and measured weight, height, and body mass index was observed in the PNS 2013 (46).

Important strengths of our analysis also deserve mention. The main one is the representativeness of our data, which allows the generalization of our findings for the Brazilian adult population. The large sample size of the research in the two years allows accurate estimates at the national level, as well as estimates, although less accurate, for other subgroups of the population. That two national health surveys have already been conducted makes it possible to evaluate the growing trend in access to health services for diagnosis and primary diabetes care.

Despite the limitations presented, this study contributes to otherwise sparse data on access to diabetes diagnosis, enabling debate on various dimensions of access to health services and their inequities, pointing to groups with greater barriers to the early detection of diabetes. Access and quality are inseparable in improving care for many health conditions, such as diabetes, being essential indicators in diagnosis and follow-up. The high percentages of diagnostic access to diabetes in the Brazilian population here described were possible, in large part, by the universal access to health care provided by the SUS. The SUS principles of universal access, comprehensiveness, and equity aim to guarantee the use and access of services by the whole population, thus including those with lower education and income, and without health insurance plans. However, as an underfinanced and developing health system, the SUS continues to struggle to ensure universal and equitable coverage, and there is much room for improvement.

In conclusion, access to screening and diagnosis of diabetes is high in Brazil, reflecting the wide access to medical consultation provided by the universal health system. However, inequities are still present, indicating the need for specific actions for specific groups, especially in rural areas and for Blacks and mixed-race groups.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: PNS/Fiocruz website (https://www.pns.icict.fiocruz.br/bases-de-dados/).

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

KS and RR contributed to the study design, data analysis, interpretation of results, and writing the manuscript. MS contributed to the study design, interpretation of results, and writing the manuscript. BD and OD'A contributed to the data interpretation and reviewing of the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1122164/full#supplementary-material

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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 30 March 2023
DOI 10.3389/fendo.2023.1143590

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Clinical Diabetes, a section of the journal Frontiers in Endocrinology

RECEIVED 13 January 2023
ACCEPTED 20 March 2023
PUBLISHED 30 March 2023

CITATION
Hu J, Zhu H, Dai Y, Liu Y, Lu Y, Zhu S, Chen L, Zhang M, Jiang T and Peng H (2023) Association between soluble neprilysin and diabetes: Findings from a prospective longitudinal study. *Front. Endocrinol.* 14:1143590. doi: 10.3389/fendo.2023.1143590

Association between soluble neprilysin and diabetes: Findings from a prospective longitudinal study

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Background: The potential role of neprilysin (NEP) in glucose metabolism has been found by basic studies but lacks population evidence. The objective of this study was to examine the association between serum NEP and diabetes in Chinese adults.

Methods: In a prospective longitudinal cohort study – the Gusu cohort (n=2,286, mean age: 52 years, 61.5% females), the cross-sectional, longitudinal, and prospective associations between serum NEP and diabetes were systemically examined by logistic regression adjusting for conventional risk factors. Serum NEP was measured at baseline using commercial ELISA assays. Fasting glucose was repeatedly measured 4 years apart.

Results: The cross-sectional analysis found a positive association between serum NEP and fasting glucose at baseline (β=0.08, *P*=0.004 for log-transformed NEP). This association persisted after controlling for the dynamic risk profiles during follow-up (β=0.10, *P*=0.023 for log-transformed NEP). The prospective analysis found that a higher level of serum NEP at baseline was associated with a higher risk of diabetes during follow-up (OR=1.79, *P*=0.039 for log-transformed NEP).

Conclusions: Serum NEP was not only associated with prevalent diabetes but also predicted the future risk of diabetes development in Chinese adults, independent of many behavioral and metabolic factors. Serum NEP may be a predictor and even a new therapeutic target for diabetes. However, the casualty and mechanisms of NEP in the development of diabetes require further investigation.

KEYWORDS

Chinese, diabetes, neprilysin, prospective longitudinal study, population epidemiology

Abbreviations: NEP, Neprilysin; GLP-1, glucagon-like peptide 1; HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; SBP, systolic blood pressure; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

10.3389/fendo.2023.1143590

Background

Neprilysin (NEP), a predominantly membrane-bound zinc-dependent type II metallopeptidase, is widely distributed in the body, including multiple tissues involved in glucose metabolisms, such as the liver, adipocytes, and pancreatic islets (1). By inactivating regulatory peptides *via* cleavage on the N-terminal side of hydrophobic residues, NEP is responsible for the breakdown of glucagon (2), and glucagon-like peptide 1 (GLP-1) (3), all of which play critical roles in glucose metabolism. These properties identified suggest a potential role of NEP in diabetes development and this hypothesis is also supported by findings from animal and human studies. For example, NEP deficiency inducted by gene knockout resulted in an increased islet β-cell mass and decreased glucose after 16 weeks of a high-fat diet in mice (4). Clinical trials found that NEP inhibition resulted in reduced hemoglobin A1c (HbA1c), fewer new-onset diabetes, and less insulin therapy in patients with diabetes (5) (6). Real-world studies also found that better glucose control were popular in patients with heart failure receiving the treatment of ARNi, a dual-acting angiotensin-receptor-neprilysin inhibitor (7). Of note, a considerable proportion of diabetic patients receiving ARNi did not get optimal glucose control (8), highlighting the unclear causality between NEP and diabetes. However, the association between circulating NEP and diabetes has been scarcely studied. A small clinical study found that urinary NEP was significantly increased in 20 patients with diabetes, compared to healthy controls (9). Another study including 144 patients with heart failure failed to observe a significant association between plasma NEP and HbA1c (10). The existing studies were mainly conducted in populations with European ancestry who have different risk profiles from Chinese. To date, no study has examined the association between circulating NEP and diabetes in Chinese population. Therefore, we aimed to examine the association between serum NEP and diabetes in a longitudinal cohort of Chinese adults in the Gusu cohort.

Methods

Participants

As detailed in the Supplementary Data (eMethods), the Gusu cohort was prospectively conducted in a traditional but economically developed district of Suzhou from January 2010 to December 2020. The study participants were randomly recruited by a cluster sampling procedure, with communities as the sampling unit. In 2010, eight communities were randomly selected as the research fields from the 39 communities in the Gusu district. All eligible participants residing in these fields were invited to participate if they were aged over 30 years, of Han ethnicity, and had lived in the area for at least 10 years. There were a total of 3,061 eligible residents in the study fields, but only 2,706 (participating rate: 88%) individuals agreed to participate in this study. After providing written informed consent, they received questionnaires and were offered free physical examination and clinical biochemical tests using blood and urine specimens under the principle of voluntary acceptance. Based on the information obtained, 208 participants were excluded from the cohort if they met at least one of the following criteria: (i) having clinical suspicion of diseases that may cause secondary hypertension (e.g., renal artery stenosis, coarctation, glomerulonephritis, pyelonephritis, pheochromocytoma, Cushing's syndrome, Conn's syndrome), (ii) self-reported history of CHD, stroke, or tumors, (iii) self-reported thyroid or parathyroid diseases, (iv) being pregnant, and (v) lacking blood samples. A total of 2,498 participants completed the baseline examination and were finally enrolled in the Gusu cohort study. Hereafter, all participants were followed every two years through 2020 for any CVD events and the survivors were invited to participate in the follow-up examination in 2014. The protocols of the Gusu cohort study were approved by the Soochow University Ethics Committee. Written informed consent was obtained from all study participants.

Figure 1 describes the selection of study participants for the current study. After excluding 212 participants with missing data on serum NEP, a total of 2286 participants were included in the cross-sectional association analysis. After further excluding 449 participants who refused to participate in the Phase II examination, 1837 participants were included in the longitudinal association analysis between serum NEP and dynamic fasting plasma glucose (FPG) during follow-up. Of these, 1668 participants free of diabetes at the Phase I examination were included in the analysis of the prospective association between baseline serum NEP and incident diabetes.

Measurement of fasting plasma glucose and definition of incident diabetes

Venous blood was drawn in the morning after a requested overnight fast (at least 8 hours). FPG was measured immediately on Hitachi 7020 automatic biochemical analyzer using commercial reagents (Kangxiang Medical Appliances, Shanghai, PR of China).

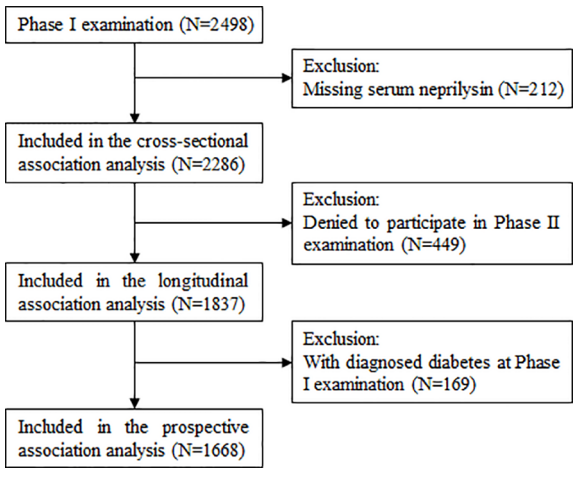

FIGURE 1
A flowchart illustrating the selection of participants and analytical plan.

In our study, diabetes was defined as FPG ≥ 7.0 mmol/L or self-reported history of physician-diagnosed diabetes with a current prescription of insulin or oral hypoglycemic medications (11). Incident diabetes was defined as free of diabetes at baseline but initiated hypoglycemic medications during follow-up or with an FPG ≥ 7.0 mmol/L at the last follow-up examination.

Measurement of serum NEP

The measurement of serum NEP was performed by skilled staff in the Jiangsu Key Laboratory of Preventive and Translational Medicine for Geriatric Diseases at Soochow University. Quantitative sandwich enzyme immunoassay (RayBiotech) was used to examine soluble NEP levels in serum samples stored at -80 °C. A standard curve was constructed and from which NEP concentrations of unknown samples were determined. Intra- and inter-assay coefficients of variation were less than 10% and 12%, respectively.

Assessment of conventional risk factors

At the baseline examination, sociodemographic information (age, sex, and education level), lifestyle risk factors (cigarette smoking and alcohol drinking), and medical history were obtained by trained staff using standard questionnaires in the Chinese language. Metabolic factors (obesity, blood pressure, glucose, and lipids) were obtained by physical examination and laboratory testing. The detailed methods of data collection were presented elsewhere (12) and in the Supplementary Data (eMethods).

Statistical analysis

All statistical analyses were conducted using R version 4.2.1. A two-tailed *P* value of less than 0.05 was considered statistically significant. Participants were divided into three groups according to tertiles of serum NEP. Their baseline characteristics were presented and compared across three groups. Serum NEP were log-transformed (log-NEP) to maximize the normality of data distribution and the generated values were used in downstream analyses.

Cross-sectional analysis

To examine the association between serum NEP and prevalent diabetes, we first constructed a median regression model in which FPG at baseline was the dependent variable and log-NEP was the independent variable, adjusting for conventional risk factors including age, sex, education level, cigarette smoking, alcohol drinking, systolic blood pressure (SBP), body mass index (BMI), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and hypoglycemic medication. Median regression was used here to account for the skewed distribution of FPG. We then similarly constructed a logistic regression model with prevalent diabetes (yes/no) as the dependent variable and serum NEP (log-NEP or categorical NEP in tertiles) as the independent variable.

Longitudinal analysis

To examine whether serum NEP at baseline was associated with dynamic FPG during follow-up, we constructed a linear mixed regression model in which repeated measures of FPG were the dependent variable, serum NEP at baseline was the independent variable, adjusting for repeated measures of conventional risk factors listed above, with participants as the random effect. The mixed model was used here to account for repeated measurements and reduce the effects of dynamic risk profiles on FPG.

Prospective analysis

To further examine whether serum NEP at baseline predicts the future risk of diabetes, we constructed a logistic regression model with diabetes at follow-up (yes/no) as the dependent variable and serum NEP at baseline was the independent variable, adjusting for covariates listed above as well as follow-up years. In this model, participants who had been already diagnosed with diabetes at baseline were excluded.

Results

Baseline characteristics of study participants

A total of 2286 participants (mean age: 52 years, 61.5% females) were included in the current study. Their baseline characteristics were shown in Table 1. Participants with a higher level of serum NEP were more likely to be drinkers and have a higher level of blood pressure and lipids but were less likely to be smokers (all $P<0.05$). No significant differences were found in the other variables listed.

The cross-sectional association between serum NEP and diabetes

Figure 2 displays a significant correlation between serum NEP and FPG at baseline (spearman r=0.052, $P=0.014$). The median regression found that after adjustment for conventional risk factors, serum NEP was still significantly associated with a higher level of FPG (β=0.08, $P=0.004$ for log-NEP). Logistic regression found that participants with a higher level of serum NEP were more likely to have diabetes (OR=1.28, $P=0.072$ for log-NEP, Figure 3).

TABLE 1 Baseline characteristics of study participants according to serum neprilysin levels.

Characteristics	Serum neprilysin, ng/mL			*P*-value for trend
	Tertile 1(~0.65)	Tertile 2(0.66~1.49)	Tertile 3(1.50~)	
No. of participants	764	759	763	–
Age, years	52.6 ± 9.3	52.0 ± 9.6	52.6 ± 9.0	0.995
Sex, males (%)	280(36.65)	307(40.45)	294(38.53)	0.449
Education, high school or above (%)	132(17.28)	173(22.79)	161(21.10)	0.064
Cigarette smoking, n (%)	188(24.61)	191(25.16)	153(20.05)	0.035
Alcohol drinking, n (%)	119(15.58)	150(19.76)	160(20.97)	0.007
Body mass index, kg/m^2	24.75 ± 3.72	24.81 ± 3.62	24.89 ± 3.72	0.468
Systolic blood pressure, mmHg	129.0 ± 16.2	129.4 ± 16.4	131.6 ± 18.1	0.003
Diastolic blood pressure, mmHg	84.0 ± 8.8	84.9 ± 9.3	86.0 ± 9.5	<0.001
Total cholesterol, mmol/L	5.14 ± 1.11	5.19 ± 1.53	5.34 ± 2.47	0.030
Triglycerides, mmol/L	1.27 ± 0.92	1.54 ± 1.55	1.57 ± 1.85	<0.001
LDL cholesterol, mmol/L	3.01 ± 0.76	2.97 ± 0.75	3.03 ± 0.76	0.662
HDL cholesterol, mmol/L	1.52 ± 0.37	1.49 ± 0.50	1.52 ± 0.46	0.805

Results are expressed as mean ± SD (standard deviation) unless otherwise noted.
P-values for trend were tested by linear regression model for continuous variables and chi-square trend test for categorical variables. LDL, low-density lipoprotein; HDL, high-density lipoprotein.

The longitudinal association between serum NEP and dynamic FPG

Table 2 shows the association between baseline serum NEP and dynamic FPG during follow-up. The linear mixed regression found that a higher level of serum NEP at baseline was significantly associated with a higher level of FPG (β=0.11, *P*=0.018 for log-NEP). This association persisted after controlling for the dynamic risk profiles (β=0.10, *P*=0.023 for log-NEP). Compared to participants with the lowest level of serum NEP, those with the highest level of serum NEP had a 0.10 mmol/L increased level of PFG (β=0.10, *P*=0.076).

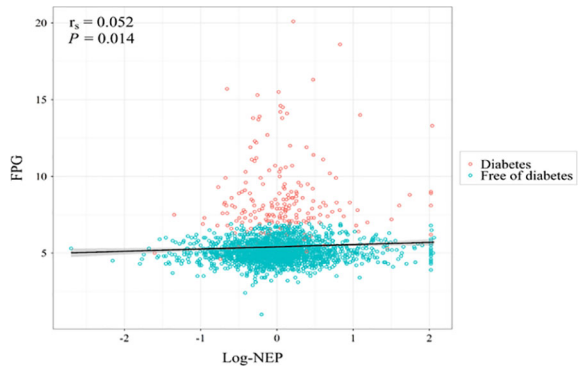

FIGURE 2
A scatterplot illustrating the association between serum neprilysin and fasting plasma glucose at baseline. Legend: The spearman correlation analysis found a significant correlation between serum neprilysin and fasting plasma glucose at baseline (r_s=0.052, *P*=0.014). Red circles indicate individuals with diabetes and blue circles indicate individuals free of diabetes at baseline. After further adjustment for age, sex, education level, cigarette smoking, alcohol consumption, body mass index, systolic blood pressure, low- and high-density lipoprotein cholesterol, and hypoglycemic medication, the association was still significant (β=0.08, *P*=0.004). FPG, fasting plasma glucose; log-NEP, log-transformed serum neprilysin; r_s, spearman correlation coefficient.

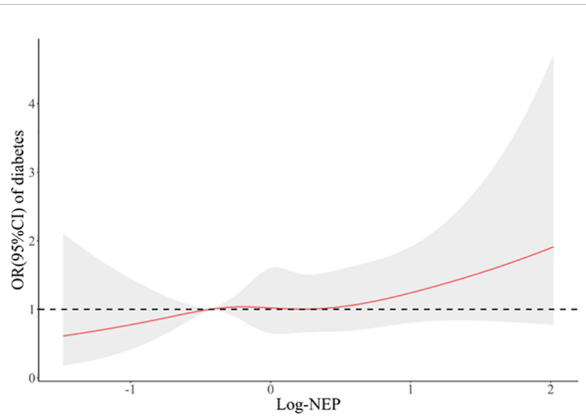

FIGURE 3
A restricted cubic spline curve illustrating the association between serum neprilysin and prevalent diabetes at baseline. Legend: A restricted cubic spline regression model was constructed with knots set at the 10th, 50th, and 90th percentiles of the distribution of serum NEP. The red line indicates the odds ratios and the gray shadow indicates the corresponding 95% confidence intervals of prevalent diabetes in association with the increasing levels of log-NEP, compared with the midpoint of the 10th percentile. Serum NEP was linearly (*P* for non-linearity=0.853) associated with a higher risk of prevalent diabetes (OR=1.28, *P*=0.072). OR, odds ratio; CI, confidence interval.

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TABLE 2 The longitudinal association between baseline serum neprilysin and dynamic fasting plasma glucose during follow-up.

Serum neprilysin (ng/mL)	Unadjusted		Adjusted*	
	β(se)	*P*-value	β(se)	*P*-value
Log-NEP	0.11(0.05)	0.018	0.10(0.05)	0.023
Categorical				
Tertile 1	Reference	–	Reference	–
Tertile 2	0.04(0.07)	0.590	0.02(0.07)	0.709
Tertile 3	0.15(0.07)	0.027	0.10(0.06)	0.076

*Adjusting for sex, education level at baseline, and repeated measures of age, cigarette smoking, alcohol consumption, body mass index, systolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol at baseline and follow-up examinations.

The prospective association between serum NEP and diabetes

In the follow-up period (mean 4.1 years, range 3.9-4.3 years), 100 of the 1668 participants free of diabetes at baseline developed new diabetes. The logistic regression found that a higher level of serum NEP at baseline was significantly associated with an increased risk of diabetes (OR=1.79, *P*=0.039 for log-NEP), independent of conventional risk factors. Compared to participants with the lowest level of serum NEP at baseline, those with the highest level of serum NEP had an 80% increased risk of diabetes during follow-up (OR=1.80, *P*=0.045, Table 3).

Discussion

In this large prospective cohort study, we found for the first time that serum NEP was not only associated with prevalent diabetes but also predicted an increased future risk of diabetes development in Chinese adults, independent of behavior and metabolic factors. Our results suggested that serum NEP could be a predictor and even a risk factor for diabetes.

In line with our study, the role of NEP in glucose metabolism has also been reported in previous studies (9, 13, 14). For example, an *in vitro* study found that NEP activity was upregulated in human dermal microvascular endothelial cells after short-term exposure to glucose (15). In animal experiments, $Nep^{+/+}$ mice displayed progressively elevated glucose levels over time, and $Nep^{-/-}$ mice exhibited improved glucose tolerance and elevated active GLP-1 levels (14). In humans, a small clinical study including 40 patients with diabetes complicated with chronic kidney disease and 20 healthy controls found that urinary NEP levels were significantly increased in patients with diabetes (9). A cross-sectional study including 318 white European males found that plasma NEP was elevated in patients with metabolic syndrome and associated with insulin resistance and obesity (16). However, these results are mainly generated from white populations and there is no evidence for the temporal association between NEP and incident diabetes, which is critical for the causal inference and clinical translation of NEP. In our study, we systemically examined the temporal relationship between serum NEP and diabetes in cross-sectional, longitudinal, and prospective aspects to rule out probable reverse causality. We found that a higher serum NEP at baseline was not only associated with higher prevalent diabetes but also predicted glucose elevation during follow-up and a higher future risk of incident diabetes. Together with prior studies, the consistent findings in our study increased the probability that elevated NEP may be a risk factor for diabetes. However, the causal association between serum NEP and diabetes still needs more evidence, from clinical trials in particular.

The mechanisms underlying the relationship between NEP and diabetes are not very clear and a better understanding of the mechanisms would improve the prevention and management of diabetes. There are several potential mechanisms through which NEP may participate in the regulation of glucose homeostasis. One possible mechanism could be the regulation of insulin secretion and glycemic homeostasis. NEP could be synthesized and expressed in islets (17), a target tissue of glucose metabolism. Inhibition of NEP could upregulate insulinotropic effects of incretin hormone GLP-1 (18) (19), suggesting the potential influence of NEP on insulin

TABLE 3 The prospective association between serum neprilysin and incident diabetes during follow-up.

Serum neprilysin (ng/ml)	Incidence (%)	Unadjusted		Adjusted*	
		OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Log-NEP	100(5.23)	1.22(0.85-1.74)	0.276	1.26(0.85-1.85)	0.249
Categorical					
Tertile 1	24(3.74)	Reference		Reference	
Tertile 2	33(5.30)	1.67(0.96-2.97)	0.075	1.71(0.96-3.09)	0.071
Tertile 3	43(6.63)	1.79(1.04-3.15)	0.039	1.80(1.02-3.24)	0.045

*Adjusting for age, sex, education level, cigarette smoking, alcohol consumption, body mass index, systolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol at baseline and follow-up years.

secretion. The second mechanism may be the contribution to insulin resistance. NEP perturbs insulin signaling and regulates the expression of the insulin receptor subunits in human subcutaneous white preadipocytes (20). NEP deficiency caused by gene knockdown could enhance insulin sensitivity and increase pancreatic β-cell function and mass in high-fat diet mice (4). Another possible mechanism may be the synergistic effects of NEP and its substrates. For example, the natriuretic peptide system also plays a crucial role in glucose metabolism (21) and the natriuretic peptides are mainly degraded by NEP. The complex role of NEP in glucose metabolism warranted further investigation to improve the precision medicine of diabetes. Recently, ARNi (sacubitril/valsartan), a compound preparation of NEP inhibitor accompanied with valsartan, has been recommended and widely used for patients with HFrEF (22). A *post-hoc* analysis from the PARADIGM trial (6) in which 3778 patients with known diabetes or previously undiagnosed diabetes with an HbA1c over 6.5% were randomized to receive either ARNi or enalapril found a greater reduction in HbA1c levels and new-onset diabetes in ARNi group compared to the enalapril group. In stark contrast, this superior blood glucose-control effect of ARNi was not significant in a real-world study in Korean patients (23). Due to the intimate interrelation between heart failure and diabetes, if NEP is proved to be one of the reliable biomarkers and core therapeutic targets for diabetes, killing two birds with one stone is undoubtedly a better treatment option. However, mechanisms through which NEP participates in diabetes need further investigation.

This study is the first to examine the prospective association between circulating NEP levels and diabetes risks in Chinese adults. The strengths included the prospective longitudinal study design, systemic analyses including cross-sectional, longitudinal, and prospective associations, and comprehensive assessment and adjustment for conventional risk factors including behavioral and metabolic factors. Some limitations should also be acknowledged. First, although some studies demonstrated a linear correlation between NEP expression and activity (24), it is still uncertain whether NEP levels in circulation perfectly correlate with biologically active tissue levels. We didn't measure NEP activity, e.g., GLP-1, in this study, and further investigation of the relationship between serum NEP concentrations and activity is required. Second, as an observational study, residual confounding still exists in our study and the causal association between NEP and diabetes is still uncertain. Finally, given the lack of ethnic diversity, the generalization of our results to other ethnic populations should be cautious.

Conclusions

Our study demonstrated that increased serum NEP was not only associated with prevalent diabetes at baseline but also predicted glucose elevation and an increased risk of diabetes development during follow-up in Chinese adults, independent of behavioral and metabolic factors. These results suggest that serum NEP may be a predictor and even a new therapeutic target for diabetes. Further investigation is urgently needed to illuminate the casualty and mechanisms of NEP in the development of diabetes.

Data availability statement

Publicly available datasets were analyzed in this study. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by the Soochow University Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

TJ and HP conceived and designed the study. JH and HZ analyzed and interpreted the data. JH drafted the manuscript. HZ collaborated in writing of the methods. YD and YLiu contributed to the revision of the manuscript. SZ contributed to the interpretation of the results. YLu and LC assisted with the data collection and analysis. TJ and HP contributed to the interpretation of the results reviewed/edited of the manuscript and gave the final approval of the version to be published, and all authors agreed to be accountable for all aspects of the work. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the National Natural Science Foundation of China (NO. 82173596, 81903384, and 81872690) and a Project of the Priority Academic Program Development of Jiangsu Higher Education Institutions. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments

Numerous organizations have provided invaluable assistance in the conduct of this study, including the Gusu Center for Disease Prevention and Control, Gusu Health Commission, the Second Affiliated Hospital of Soochow University, and the eight community health service centers. Most importantly, the authors gratefully acknowledge the continued cooperation and participation of the members of the Gusu cohort study and their families. Without their contribution, this research would not have been possible.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1143590/full#supplementary-material

SUPPLEMENTARY DATA SHEET

eMethods: A detailed description of the methods of participants selection and data collection.

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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 09 June 2023
DOI 10.3389/fendo.2023.1186702

OPEN ACCESS

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RECEIVED 15 March 2023
ACCEPTED 23 May 2023
PUBLISHED 09 June 2023

CITATION
Wang N, Li Y and Guo C (2023) Waist-corrected BMI predicts incident diabetes mellitus in a population-based observational cohort study.
Front. Endocrinol. 14:1186702.
doi: 10.3389/fendo.2023.1186702

Waist-corrected BMI predicts incident diabetes mellitus in a population-based observational cohort study

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Introduction: Waist-corrected body mass index (wBMI), which combines BMI and waist circumference (WC) measurements, has proven superior to either measure alone for predicting obesity but has not yet been applied to the prediction of diabetes mellitus (DM).

Methods: Over a 5-year period, 305,499 subjects were eligible for this study based on citizen health check-ups in the Tacheng Area of northwest China. Diagnosis of DM was defined as the end point.

Results: After exclusion, a total of 111,851 subjects were included in the training cohort and 47,906 in the validation cohort. Participants of both sexes with wBMI in the upper quartiles had significantly higher incidence of DM than those with wBMI in the lower quartiles (log-rank χ^2 = 236, p< 0.001 for men; log-rank χ^2 = 304, p< 0.001 for women). After adjusting for multiple variables, WC, BMI, wBMI, and waist-to-height ratio (WHtR) were all independent predictors for diabetes. In men, the adjusted hazard ratios (HRs) of wBMI for diabetes for the second, third, and fourth quartiles were 1.297 [95% CI: 1.157, 1.455], 1.664 [95% CI: 1.493, 1.853], and 2.132 [95% CI: 1.921, 2.366], respectively, when compared with the first quartile. In women, they were 1.357 [95% CI: 1.191, 1.546], 1.715 [95% CI: 1.517, 1.939], and 2.262 [95% CI: 2.010, 2.545], respectively. Compared with WC, BMI, and WHtR, wBMI had the highest C-index in both men (0.679, 95% CI: 0.670, 0.688) and women (0.730, 95% CI: 0.722, 0.739). Finally, a nomogram was constructed to predict incident DM based on wBMI and other variables. In conclusion, wBMI had the strongest predictive capacity for incident DM when compared with WC, BMI, and WHtR, especially in women.

Discussion: This study provides a reference for advanced investigation of wBMI on DM and other metabolic diseases in the future.

KEYWORDS

diabetes mellitus, waist-corrected body mass index, body mass index, waist circumference, waist-to-height ratio

1 Introduction

Overweight and obesity are well-known risk factors for incident type 2 diabetes mellitus (T2DM). Body mass index (BMI) is the most common index for assessing overall adiposity because it is measured easily and is strongly associated with total body fat mass. High BMI has been associated with increased risk of T2DM (1). In study of Pima Indians, the age-adjusted risk ratio for developing diabetes was 90.3 for individuals with BMI ≥40 kg/m^2 compared to those with BMI<20 kg/m^2 (2). In a study of female nurses, the risk for incident diabetes increased 93.2-fold in individuals whose BMI increased from<22 kg/m^2 at age 18 to ≥35.0 kg/m^2 at age 30–55, compared to individuals who maintained a steady weight (3). BMI has long been a traditional, routine, and important indicator to be monitored in patients with obesity or hyperglycemia.

However, recent studies have demonstrated the limitations of BMI. It evaluates general obesity but does not account for body fat distribution (4). While some studies have associated BMI with abdominal obesity, others show divergence between the two measures, suggesting that BMI may not accurately reflect the distribution of fat in the body (5). Individuals who have abdominal obesity but are lean according to BMI show increased prevalence of cardiovascular disease and diabetes (6). Other studies have shown that a larger waist circumference (WC) increases the future risk of cardiovascular disease and diabetes by two- to threefold for a given BMI (7, 8).

Because of the aforementioned shortfalls of BMI in evaluating adipose distribution, other indexes have been adopted to assess body shape, including WC, WaisttoHip Ratio, WaisttoHeight Ratio (WHtR), Body Adiposity Index, A Body Shape Index, and Visceral adiposity Index (9–16). Recently, waist-corrected BMI (wBMI), a new and simple indicator combining BMI and WC, was developed by Antonini-Canterin et al. in 2018 to evaluate overfat and obese patients. It has the advantage of considering global fat mass in conjunction with fat distribution and therefore could overcome the limitations of BMI or WC alone. It is calculated by the equation below (17), in which body weight (BW) is measured in kg, WC in m, and height (H) in m.

$$wBMI = \frac{BW * WC}{H^2}$$

Studies of wBMI demonstrated that it outperformed BMI, WC, and WHtR most dramatically in predicting adverse cardiac remodeling patterns, increased arterial stiffness, increased insulin resistance, and unfavorable lipid profile (17). Moltrer et al. evaluated the accuracy of wBMI for classifying overfat and obese patients identified by fat mass percentage in comparison to BMI, WC, and WHtR. They found that wBMI had the greatest discriminating capacity for female patients. wBMI is therefore an accurate indicator for healthcare professionals to identify overfat and obese patients and monitor them during the course of treatment (18).

However, the predictive effect of wBMI on diabetes has not been studied. Considering the advantages offered by wBMI in identifying overfat and obese patients, this study was designed to compare the predictive capacity of wBMI with BMI, WC, and WHtR (12, 19). The present study compared concordance indexes (C-index) of Cox regression analysis across body composition measures and constructed a predictive nomogram including wBMI and other important variables.

2 Materials and methods

2.1 Data source

Tacheng Area is a region of Xinjiang Province in northwest China with a population of 1.1 million. All citizens in this area received free yearly health checkups beginning in 2016 as part of a social welfare program encompassing 608 health checkup organizations in seven cities. The present study analyzed health checkup data from 1 January 2016 to 31 December 2020. During this time, 305,499 adult individuals (18–117 years old) received annual checkups.

The study was approved by the Ethical Review Committee of Shengjing Hospital of China Medical University (No. 2021PS633K). Informed consent was waived due to the non-interventional study design. The study was conducted in accordance with guidelines set forth in the Declaration of Helsinki.

2.2 Study design

Participants aged more than 18 years old were enrolled, their age, sex, height, weight, and WC were recorded at every visit. Fasting plasma glucose (FPG), serum lipids, and liver and kidney function were also examined. Information on diabetes family history, alcohol consumption, previous disease history, current disease status, present medication, and habits of smoking, drinking, and exercise were collected in self-reported questionnaires at the first visit in 2016.

Subjects were excluded if their baseline age was<18 years; they had a history of diabetes, malignancy, severe liver or kidney dysfunction, or hyperthyroidism or other endocrine disease that affects blood glucose; they took medication that affects glucose levels (e.g., glucocorticoids, antidepressants); they had fewer than three visits or were missing data; and if they were pregnant.

2.3 Definitions of variables

There were four means of classifying patients as diabetic: self-reported, FPG ≥7.0 mmol/L, HbA1c ≥6.5%, or use of diabetic medications (including special diet, weight control medication, oral medication, insulin injection, or intake of Chinese traditional medicine).

Tobacco smoking was classified as “never” (fewer than 100 cigarettes smoked in lifetime), “ever” (smoked at least 100 cigarettes in their lifetime but has quit smoking for at least the previous 12 months), or “current smoker” (including daily smokers and non-daily or occasional smokers). Alcohol history was classified as

"never," "mild drinker" (<30 g alcohol/day), or "heavy drinker" (≥30 g alcohol/day). Physical exercise was defined as more than 30 min exercise at a time, and the frequency of physical exercise was classified as "seldom" (<1 time/week), "occasionally" (1–3 times/week), and "frequently" (>3 times/week). Diet pattern was self-reported as either "Mediterranean" (predominantly vegetables, fruits, low-fat dairy, and legumes), "meat" (predominantly red and processed meat products), or "balanced." Height, weight, and WC were measured according to standard methods. BMI was calculated as weight in kilograms divided by height (in meters) squared. WHtR was calculated as WC in meters divided by height in meters.

2.4 Statistical analysis

Continuous data are presented as mean (SD) and categorical variables as frequencies. Continuous variables were compared between two groups using an independent samples *t*-test after Leneve's test for equality of variance. χ^2 test was used to compare categorical variables. Predictive analysis of wBMI, BMI, WC, and WHtR for incident DM was analyzed by Cox regression after adjusting for confounding variables. Predictive abilities of the various body composition measures were compared by C-indexes. A nomogram was developed using weighted estimators corresponding to each covariate derived from fitted Cox regression coefficients and estimates of variance. Validation of the nomogram was assessed by a calibration curve. A calibration plot was generated to compare the actual Kaplan–Meier survival estimates with predicted survival probabilities. Cox regression and the nomogram were calculated in R software (version 4.0.3) with survival (version 3.4-0), rsm (version 2.10.3), survcomp (1.48.0), and survminer (version 0.4.9) packages. Statistical significance was set at $p< 0.05$.

3 Results

3.1 Baseline characteristics

Individuals were excluded for missing wBMI information (n = 14,814); having diabetes at baseline (n = 36,532); being younger than 18 years old (n = 40,137); missing data for FPG, serum lipids, or liver and kidney function (n = 42,050); having fewer than three visits (n = 18,601); and other reasons (n = 3,608). After exclusion, 159,757 adult subjects were included in this study. Subjects were randomly divided into training and validation cohorts by 70:30 ratio to yield 111,851 training subjects and 47,906 validation subjects. There were 52,758 men and 59,093 women, the mean age was 44.9 ± 14.0 years, and the mean follow-up time was 3.3 ± 0.7 years (range, 0.3–4.9 years) in the training cohort. There were 22,630 men and 25,276 women, the mean age was 45.8 ± 13.6 years, and the mean follow-up time was 3.4 ± 0.7 years (range, 0.2–5.0 years) in the validation cohort). Supplementary Figure S1 shows the participant selection process. Supplementary Table S1 presents the baseline characteristics of subjects in validation cohort.

Because wBMI differs between men and women (18), participants were divided by sex. Compared to non-diabetic patients, at baseline, DM patients of both sexes were older (52.1 ± 12.8 years for men, 55.2 ± 12.4 years for women); had higher systolic blood pressure (127.8 ± 10.5 mmHg for men and 122.8 ± 12.0 mmHg for women) and FPG (5.48 ± 0.84 mmol/L for men and 5.51 ± 0.82 mmol/L for women); larger WC (93.1 ± 12.6 cm for men, 88.2 ± 12.2 cm for women), BMI (27.0 ± 4.0 kg/m^2 for men, 26.6 ± 4.4 kg/m^2 for women), wBMI (25.4 ± 6.9 kg/m for men, 23.7 ± 7.1 kg/m for women), and WHtR (0.59 ± 0.53 for men, 0.55 ± 0.09 for women); higher percentage of DM family history (4.3% for men, 4.1% for women) and history of high blood pressure (HBP) (20.9% for men, 21.7% for women); lower education level (12.9% of men and 10.6% of women received >9 years of education); and less physical exercise (6.8% of men and 6.1% of women were frequently active) (Table 1).

3.2 wBMI is a risk factor of incident DM

Unadjusted 2- and 4-year DM incidence in this cohort was 2.9% and 6.9%, respectively, in men 2.5% and 5.5% in women. As shown in Figure 1, participants of both sexes with wBMI in the upper quartiles had significantly greater DM incidence than those with wBMI in the lower quartiles (log-rank $\chi^{2\ =}$ 236, p< 0.001 for men; log-rank $\chi^{2\ =}$ 304, p< 0.001 for women).

Univariate Cox regression models showed that wBMI was a significant predictor of incident DM (men: Q2: HR 1.484 [95% CI: 1.326, 1.662]; Q3: HR 2.080 [95% CI: 1.870, 2.315]; Q4: HR 2.829 [95% CI: 2.554, 3.134]; women: Q2: HR 1.532 [95% CI: 1.294, 1.814]; Q3: HR 2.371 [95% CI: 2.027, 2.773]; Q4: HR 3.196 [95% CI: 2.749, 3.717]). The HRs increased with elevated wBMI quartiles for

TABLE 1 Baseline characteristics of participant by incident diabetes mellitus in men and women.

	Male			Female		
	DM	NDM	p	DM	NDM	p
n	3,657	49,101		3,272	55,821	
Age (years)	52.1 (12.8)	45.2 (13.9)	<0.001	55.2 (12.4)	45.2 (13.2)	<0.001
Pulse (rpm)	76.4 (18.6)	75.5 (25.1)	0.035	77.5 (21.4)	76.4 (26.5)	0.030
SBP (mmHg)	127.8 (10.5)	125.4 (10.3)	<0.001	122.8 (12.0)	121.5 (11.7)	0.002

(Continued)

TABLE 1 Continued

	Male			Female		
	DM	NDM	p	DM	NDM	p
DBP (mmHg)	80.4 (9.5)	78.4 (8.2)	<0.001	75.8 (9.3)	75.5 (8.4)	0.331
WC (cm)	93.1 (12.6)	88.8 (12.0)	<0.001	88.2 (12.2)	82.8 (12.0)	<0.001
BMI (kg/m^2)	27.0 (4.0)	25.5 (3.8)	<0.001	26.6 (4.4)	24.6 (4.1)	<0.001
wBMI (kg/m^2*m)	25.4 (6.9)	22.9 (6.0)	<0.001	23.7 (7.1)	20.7 (6.0)	<0.001
WHtR	0.59 (0.53)	0.53 (0.48)	0.01	0.55 (0.09)	0.52 (0.50)	<0.001
DM family history (Yes, % (n))	4.4 (160)	2.0 (1,001)	<0.001	4.1 (135)	2.1 (1,169)	<0.001
Urban (yes, % (n))	37.8 (1,382)	39.1 (19,201)	0.106	38.6 (1,263)	39.2 (21,910)	0.459
>9-year education (Yes, % (n))	12.9 (472)	14.8 (7,286)	0.001	10.6 (344)	15.2 (8,467)	<0.001
Exercise (% (n))			<0.001			<0.001
Seldom	82.8 (3,028)	84.6 (41,560)		83.2 (2,725)	85.4 (47,683)	
Occasionally	10.4 (380)	4.7 (2,300)		10.5 (347)	3.9 (2,200)	
Frequently	6.8 (249)	10.7 (5,241)		6.1 (200)	10.6 (5,938)	
Diet (% (n))			0.015			0.150
Mediterranean	2.0 (73)	2.3 (1,124)		3.1 (101)	3.3 (1,839)	
Balance	95.4 (3,490)	94.3 (46,319)		95.0 (3,107)	94.2 (52,609)	
Meat	2.6 (94)	3.4 (1,658)		2.0 (64)	2.5 (1,373)	
Smoker (% (n))			0.004			0.049
Never	56.3 (2,058)	57.2 (28,105)		98.6 (3,227)	99.0 (55,279)	
Ever	5.4 (197)	4.2 (2,076)		0.09 (3)	0.1 (66)	
Present	38.3 (1,402)	38.6 (18,920)		1.3 (42)	0.9 (476)	
Drinker (% (n))			0.005			0.021
Never	60.5 (2,212)	62.2 (30,534)		96.5 (3,158)	95.8 (53,469)	0.370
Mild	34.2 (1,252)	33.6 (16,491)		3.2 (105)	4.0 (2,259)	0.487
Heavy	5.3 (193)	4.2 (2,076)		0.3 (9)	0.2 (93)	Ref
HBP (Yes, % (n))	20.9 (763)	5.6 (2734)	<0.001	21.6 (707)	4.1 (2,310)	0.004
CHD (Yes, % (n))	0.1 (4)	0.08 (41)	0.619	0.1 (4)	0.1 (57)	0.734
Cerebral stroke (Yes, % (n))	0.3 (10)	0.1 (58)	0.026	0.3 (11)	0.2 (105)	0.063
FPG (mmol/L)	5.48 (0.84)	4.97 (0.71)	<0.001	5.51 (0.82)	4.92 (0.68)	<0.001
ALT (U/L)	29.5 (21.7)	27.3 (18.6)	<0.001	26.6 (17.4)	20.8 (14.4)	<0.001
AST (U/L)	24.5 (11.4)	23.8 (11.7)	<0.001	23.1 (12.8)	21.7 (10.7)	<0.001
SCr (μmol/L)	78.1 (23.9)	77.3 (21.6)	0.011	69.0 (22.8)	66.2 (21.9)	<0.001
TC (mmol/L)	4.78 (1.25)	4.66 (1.21)	<0.001	4.83 (1.30)	4.58 (1.20)	<0.001
TG (mmol/L)	1.81 (1.35)	1.49 (1.10)	<0.001	1.64 (1.12)	1.25 (0.90)	<0.001
LDL (mmol/L)	2.78 (1.02)	2.70 (0.98)	<0.001	2.77 (1.04)	2.60 (0.96)	<0.001
HDL (mmol/L)	1.43 (0.57)	1.46 (0.59)	0.008	1.50 (0.59)	1.54 (0.58)	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumstance; BMI, body mass index; wBMI, waistcorrected BMI; WHtR, WaisttoHeight Ratio; DM, diabetes mellitus; HBP, hypertension; CHD, coronary heart disease; FPG, fast plasma glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SCr, serum creatinine; TC, total cholesterol; TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

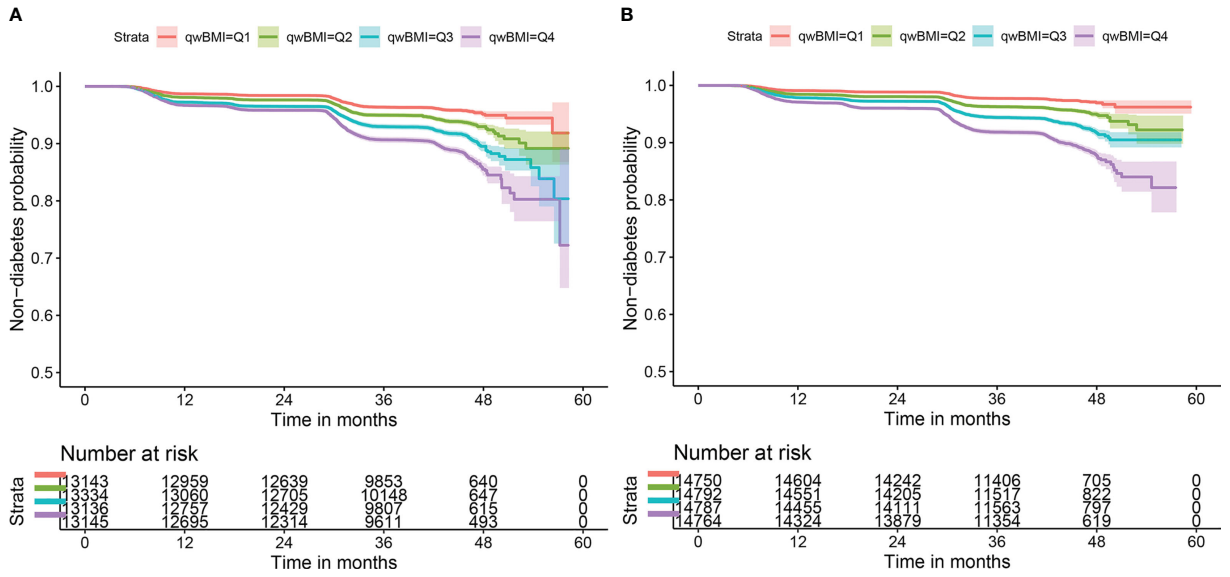

FIGURE 1
Kaplan–Meier survival curves of non-diabetes by wBMI quartiles in both sexes. Incident diabetes mellitus risk increases with wBMI quartiles in **(A)** men and **(B)** women. Log-rank χ^2 = 236, p< 0.001 for men; log-rank χ^2 = 304, p< 0.001 for women. wBMI, waist-corrected body mass index.

both sexes (Table 2). Age, DM family history, FPG, education years, current habits of smoking and exercise, and diagnosis of HBP and cerebral stroke were statistically significant for incident DM and were used to adjust for incident DM in the following multivariable Cox regression models.

After adjusting for multiple variables, WC, BMI, wBMI, and WHtR were still independent predictors for diabetes in both sexes, along with age, DM family history, FPG, HBP status, education years, and exercise habits. Notably, the adjusted HRs of wBMI for diabetes for the second, third, and fourth quartiles were 1.297 [95% CI: 1.157, 1.455], 1.664 [95% CI: 1.493, 1.853], and 2.132 [95% CI: 1.921, 2.366], respectively, when compared with the first quartile in men, and 1.357 [95% CI: 1.191, 1.546], 1.715 [95% CI: 1.517, 1.939], and 2.262 [95% CI: 2.010, 2.545] in women. Interestingly, HRs were higher in women than in men in models for WC, BMI, wBMI, and WHtR (Table 2, Figure 2).

3.3 wBMI is a better predictor of DM than other body composition measures

To compare the predictive accuracy of variables, univariable Cox regression was used to calculate the C-index of WC, BMI, wBMI, and

TABLE 2 Hazard ratios of WC, BMI, wBMI and WHtR by incident DM in men and women.

	Male				Female			
	Model 1		Model 2		Model 1		Model 2	
	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p
BMI						<0.001		<0.001
Q1	Ref	<0.001	Ref		Ref		Ref	
Q2	1.379 (1.239, 1.535)	<0.001	1.249 (1.122, 1.390)	<0.001	1.684 (1.484,1.911)	<0.001	1.382 (1.217, 1.568)	<0.001
Q3	1.824 (1.646, 2.022)	<0.001	1.521 (1.371, 1.686)	<0.001	2.453 (2.177,2.765)	<0.001	1.679 (1.489, 1.894)	<0.001
Q4	2.477 (2.248, 2.729)	<0.001	1.864 (1.690, 2.056)	<0.001	3.626 (3.236,4.064)	<0.001	2.189 (1.950, 2.457)	<0.001
WC		<0.001		<0.001		<0.001		<0.001
Q1	Ref		Ref		Ref		Ref	
Q2	1.479 (1.323, 1.652)	<0.001	1.329 (1.189, 1.4856)	<0.001	1.566 (1.384,1.772)	<0.001	1.323 (1.169,1.498)	<0.001

(Continued)

TABLE 2 Continued

	Male				Female			
	Model 1		Model 2		Model 1		Model 2	
	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p
Q3	1.905 (1.713, 2.119)	<0.001	1.579 (1.419, 1.757)	<0.001	2.335 (2.084,2.617)	<0.001	1.657 (1.478,1.859)	<0.001
Q4	2.756 (2.491, 3.049)	<0.001	2.184 (1.972, 2.420)	<0.001	3.463 (3.099,3.868)	<0.001	1.968 (1.757,2.204)	<0.001
wBMI		<0.001				<0.001		<0.001
Q1	Ref		Ref		Ref		Ref	
Q2	1.484 (1.326, 1.662)	<0.001	1.297 (1.157, 1.455)	<0.001	1.684 (1.484,1.911)	<0.001	1.357 (1.191, 1.546)	<0.001
Q3	2.080 (1.870, 2.315)	<0.001	1.664 (1.493, 1.853)	<0.001	2.453 (2.177,2.765)	<0.001	1.715 (1.517, 1.939)	<0.001
Q4	2.829 (2.554, 3.134)	<0.001	2.132 (1.921, 2.366)	<0.001	3.626 (3.236,4.064)	<0.001	2.262 (2.010, 2.545)	<0.001
WHtR		<0.001				<0.001		<0.001
Q1	Ref		Ref		Ref		Ref	
Q2	1.447 (1.300, 1.611)	<0.001	1.296 (1.163, 1.443)	0.037	1.566 (1.384,1.772)	<0.001	1.372 (1.217,1.547)	<0.001
Q3	1.969 (1.784, 2.173)	<0.001	1.554 (1.407, 1.716)	<0.001	2.335 (2.084,2.617)	<0.001	1.675 (1.487, 1.887)	<0.001
Q4	2.743 (2.488, 3.025)	<0.001	1.889 (1.710, 2.086)	<0.001	3.463 (3.099,3.868)	<0.001	1.947 (1.741, 2.178)	<0.001

Model 1, unadjusted for variables.
Model 2, adjusted for age, DM family history, FPG, education years, current habit of smoking and exercise, with diagnosis of HBP and cerebral stroke.
WC in men: Q1: ≤81.0; Q2: 81.1–89.0; Q3: 89.1–96.0; Q4: ≥96.1; in women: Q1: ≤75.0; Q2: 75.1–82.0; Q3: 82.1–90.0; Q4: ≥90.1.
BMI in men: Q1: ≤22.9; Q2: 23.0–25.3; Q3: 25.4–27.8; Q4: ≥27.9; in women: Q1: ≤21.9; Q2: 22.0–24.2; Q3: 24.3–27.0; Q4: ≥27.1.
wBMI in men: Q1: ≤18.8; Q2: 18.9–22.3; Q3: 22.4–26.4; Q4: ≥26.5; in women: Q1: ≤16.7; Q2: 16.8–19.9; Q3: 20.0–23.9; Q4: ≥24.0.
WHtR in men: Q1: ≤0.48; Q2: 0.49–0.52; Q3: 0.53–0.57; Q4: ≥0.58; in women: Q1: ≤0.47; Q2: 0.48–0.52; Q3: 0.53–0.56; Q4: ≥0.57.

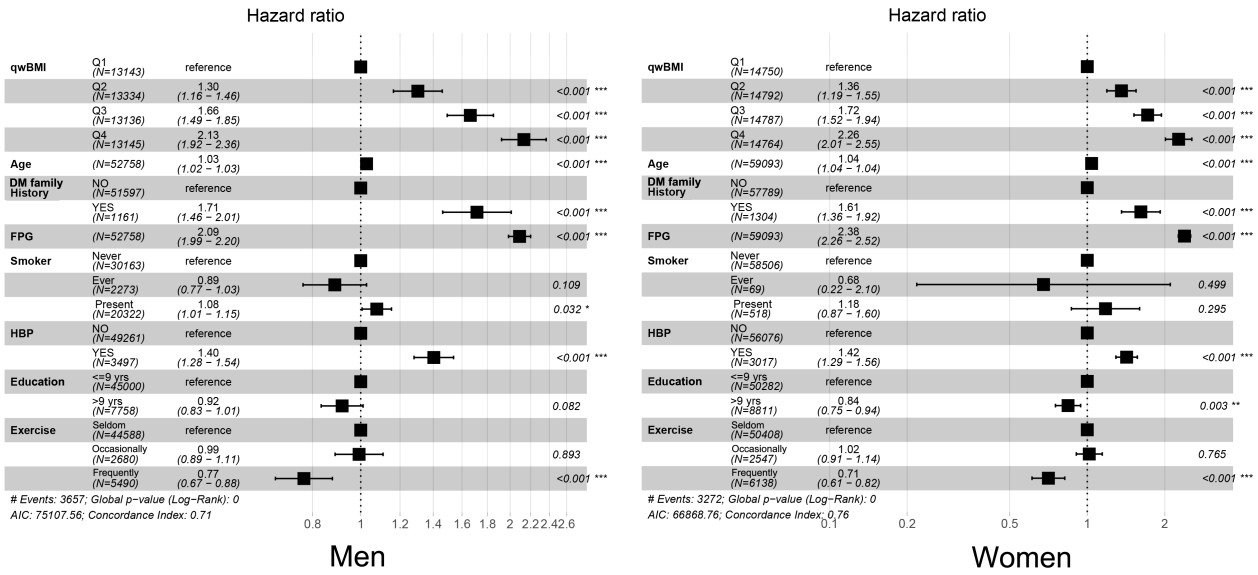

FIGURE 2
Forest plots of multivariable Cox regression results. After regression, quartiles of wBMI, age, DM family history, FPG, HBP status, education years, and exercise frequency were independent predictors for diabetes in men (left) and women (right). wBMI, waist-corrected body mass index; DM, diabetes mellitus; FPG, fasting plasma glucose; HBP, hypertension. *p< 0.05; **p< 0.01; ***p< 0.001.

WHtR (Figure 3). wBMI had the highest C-index of all the predictors: 0.679 in men and 0.730 in women (men: 95% CI 0.670–0.688; women: 95% CI 0.722–0.739) (Figure 3). In men, wBMI was significantly different from BMI (p< 0.001) and WHtR (p< 0.001) but not from WC (p = 0.435). In women, wBMI was significantly different from WC (p = 0.0234), BMI (p< 0.001), and WHtR (p< 0.001). Notably, all C-indexes were higher in women than in men.

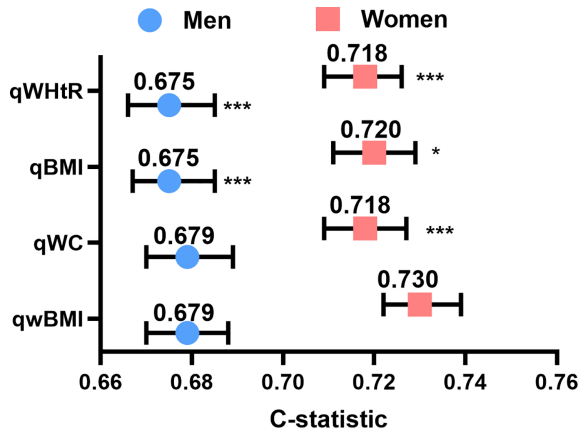

FIGURE 3
Concordance indexes of quartiles of wBMI, BMI, WC, and WHtR for both sexes. Compared to the other body composition measures, wBMI had the highest concordance in both men (left) and women (right). *p<0.05, ***p<0.001 *vs.* wBMI. qwBMI, quartile of waist-corrected body mass index; qWC, quartile of waist circumference; qBMI, quartile of body mass index; qWHtR, quartile of waist-to-height ratio.

3.4 Nomogram of wBMI for incident DM

We constructed a nomogram for incident DM in men and women that included the significant predictors identified by multivariable Cox analysis (Figure 4). Details of the individual prognostic scores of each risk factor are listed in Supplementary Tables S2; S3. The total nomogram score was determined based on the sum of individual scores. For example, a male patient with age 60 years (40 points), wBMI of 26.0 (15 points), no DM family history (0 points), history of hypertension (10 points), education<9 years (3 points), FPG of 6.0mmol/L (78 points), and who seldom exercises (8 points) would have a total score of 154 points. The subjects' 2-year non-DM probability would be 90%, and the 4-year non-DM probability would be 70%.

The C-index was 0.709 (95% CI: 0.700, 0.718, p< 0.001) for men and 0.759 (95% CI: 0.750, 0.767, p< 0.001) for women in the training cohort and 0.720 (95% CI: 0.707, 0.733, p< 0.001) for men and 0.738 (95% CI: 0.724, 0.752, p< 0.001) for women in the validation cohort, which indicates a medium discrimination ability of the model. A calibration plot was generated to assess the difference between nomogram-predicted and observed diabetes probability of the training and validation cohorts. The calibration curves showed high consistency between predicted and observed non-DM probabilities in both men and women when predicting 2- and 4-year non-diabetes probability both in the training (Figures 5A–D) and validation (Figures 5E–H) cohorts. In summary, the nomogram for DM showed acceptable discriminative and calibrating performance. We built an online calculator to predict incident DM probability based on our model, including variables of wBMI quartile, age, DM family history, FPG, hypertension history, education level, and physical exercise. The nomograms can be accessed at: https://huairen145.shinyapps.io/incident_DM_in_men/ for men and https://huairen145.shinyapps.io/DynNomapp/for women.

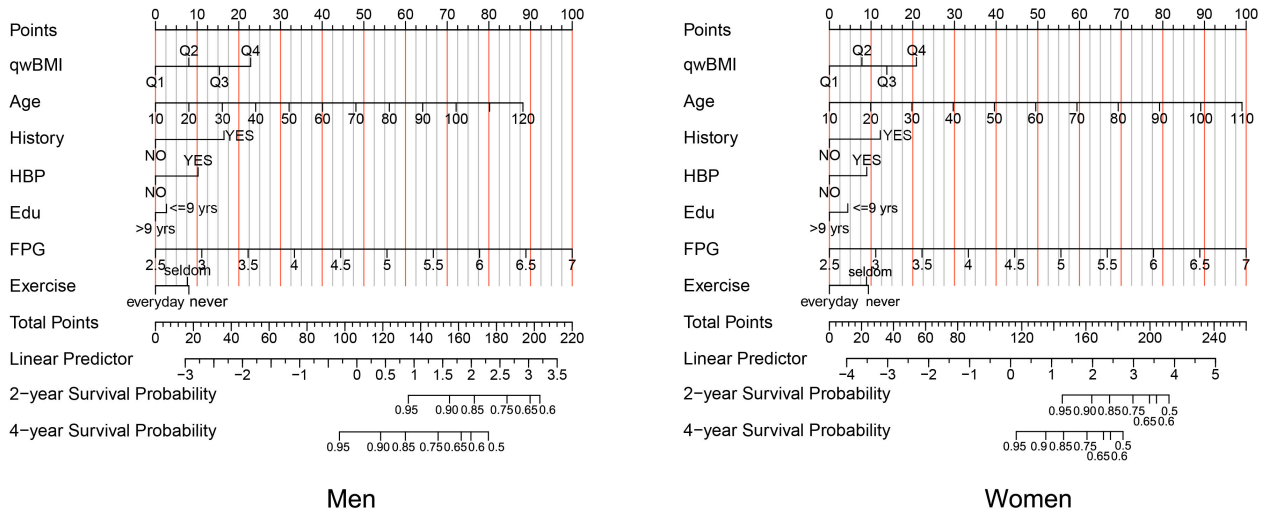

FIGURE 4
A nomogram for prognostic prediction of non-DM using qwBMI in men (left) and women (right). A male patient aged 60 years (40 points) with wBMI of 26.0 (15 points), no DM family history (0 points), a history of hypertension (10 points), education<9 years (3 points), FPG 6.0 mmol/L (78 points), and who seldom exercises (8 points) would have 154 total points. A line is drawn downward from the total points axis to the survival axes to determine probability of 2-year non-DM (approximately 90%) and 4-year non-DM (approximately 70%). DM, diabetes mellitus; qwBMI, quartile of waist-corrected body mass index; FPG, fasting plasma glucose; HBP, hypertension.

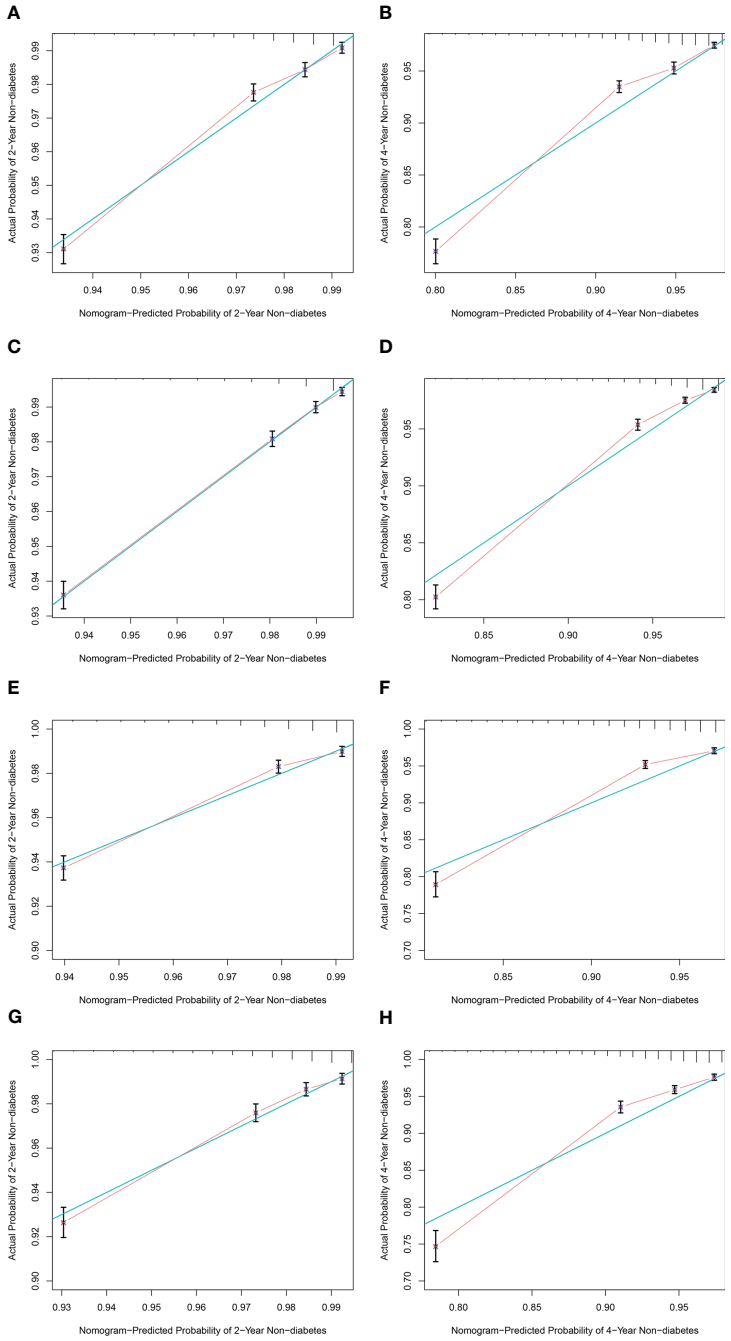

FIGURE 5
Calibration curves for the nomogram of both sexes. **(A, B)** Calibration curves of 2- and 4-year non-DM probability for male subjects in the training cohort. **(C, D)** Calibration curves of 2- and 4-year non-DM probability for female subjects in the training cohort. **(E, F)** Calibration curves of 2- and 4-year non-DM probability for male subjects in the validation cohort. **(G, H)** Calibration curves of 2- and 4-year non-DM probability for female subjects in the validation cohort. The green line indicates the ideal reference line where predicted probabilities would match observed survival rates. Red dots represent the performance of the nomogram and were calculated by bootstrapping. The closer the solid red line is to the green line, the more accurate the model's predictions. DM, diabetes mellitus.

4 Discussion

In the present study of subjects in Tacheng Area in China, wBMI was a simple and important measure for predicting incident DM. The probability of developing DM increased for patients with wBMI in higher quartiles. When compared with C-indexes of WC, BMI, and WHtR, wBMI better predicted DM, especially for women. Finally, a nomogram was developed using wBMI and other important variables. This was the first large cohort study of the association of wBMI with incident DM.

BMI and WC are widely used and important clinical anthropometric parameters, especially for metabolic disease. Typically, BMI and WC are used separately to evaluate the impacts of body fat and shape on diabetes. The present findings

showed that BMI, WC, and WHtR were all good predictors of incident DM, but a new indicator derived from the combination of BMI and WC (wBMI) was able to predict DM risk more effectively than other indexes, especially in women. BMI accounts for body fat mass but not distribution; WC and WHtR account for body fat distribution more than mass. The new index, wBMI, reflects both mass and distribution (17, 18), which may explain its advantage in predicting DM. Other studies have described the advantages of using both BMI and WC together, but did not use a unique indicator that combined them (20, 21).

In a previous study, wBMI, BMI, WC, and WHtR all showed good accuracy in identifying patients with insulin resistance, with wBMI having the largest area under curve (17). Insulin resistance is the mechanism underlying T2DM, so the strong association of wBMI with insulin resistance motivated us to further explore the relationship between wBMI and DM. Here, we demonstrated a definite prognostic function of wBMI for incident DM. wBMI and WC both outperformed BMI and WHtR when predicting DM in men, and wBMI was the strongest indicator in women. This sex difference was in accordance with a previous study (18).

Several limitations of this study need to be considered. DM was defined according to FPG, which is not as reliable as an oral glucose tolerance test. In addition, the current study only entailed a 4- to 5-year follow-up period. A follow-up study should be conducted to observe the longer-term occurrence of DM. Meanwhile, because of health checkup data limitation, we did not collect consumption of supplements that affected blood glucose (e.g., chromium). However, the large sample size and high follow-up rate in this study can reduce bias. Because this is the first investigation of predictive effects of wBMI on incident DM, it can serve as a reference for future studies.

In conclusion, incident DM risk increased with elevated quartiles of wBMI. wBMI had the strongest advantage for predicting DM when compared with WC, BMI, and WHtR, especially in women. A nomogram was developed according to wBMI and other variables identified as significant in multivariable regression analysis. This is the first large-sized cohort study on the association of wBMI with incident DM.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Review Committee of Shengjing Hospital of China Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

NW collected data, conceived and designed the experiments, analyzed data, and wrote the manuscript. YL collected data, conceived the experiment, and revised the manuscript. CG collected data, conceived and designed the experiments, and revised the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by Natural Science Foundation of Liaoning Province (Nos. 2020-MS-149 and 2019-ZD-0786) and Science and Technology Talent Program of Shenyang (No. RC200442).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1186702/full#supplementary-material

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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 15 June 2023
DOI 10.3389/fendo.2023.1185719

OPEN ACCESS

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RECEIVED 13 March 2023
ACCEPTED 30 May 2023
PUBLISHED 15 June 2023

CITATION
Herman WH and Schillinger D (2023) Rethinking diabetes in the United States. *Front. Endocrinol.* 14:1185719. doi: 10.3389/fendo.2023.1185719

Rethinking diabetes in the United States

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Despite the availability of effective medical treatments, the diabetes epidemic has accelerated in the United States, efforts to translate treatments into routine clinical practice have stalled, and health inequities have persisted. The National Clinical Care Commission (NCCC) was established by the Congress to make recommendations to better leverage federal policies and programs to more effectively prevent and control diabetes and its complications. The NCCC developed a guiding framework that incorporated elements of the Socioecological and Chronic Care Models. It gathered information from both health-related and non-health-related federal agencies, held 12 public meetings, solicited public comments, met with interested parties and key informants, and performed comprehensive literature reviews. The final report of the NCCC was transmitted to the Congress in January 2022. It called for a rethinking of the problem of diabetes in the United States, including the recognition that the lack of progress is due to a failure to confront diabetes as both a complex societal problem as well as a biomedical problem. To prevent and control diabetes, public policies and programs must be aligned to address both social and environmental determinants of health and health care delivery as they impact diabetes. In this article, we discuss the findings and recommendations of the NCCC as they relate to the social and environmental factors that influence the risk of type 2 diabetes and argue that the prevention and control of type 2 diabetes in the U.S. must begin with concrete population-level interventions to address social and environmental determinants of health.

KEYWORDS

socioecological model, social determinants of health, diabetes prevention, federal government, health policy

Introduction

Despite evidence that lifestyle and medication interventions can delay or prevent the development of type 2 diabetes; that safe and effective treatments can control glucose, blood pressure, and lipid levels; and that targeted and appropriately timed interventions can slow the progression and reduce the impact of microvascular, neuropathic, and cardiovascular complications, the diabetes epidemic has accelerated in the United States, efforts to

translate treatments into routine clinical practice have stalled, and health inequities have persisted. Between 2003 and 2020, the age-adjusted prevalence of diabetes among U.S. adults 18 years of age and older increased from 10.2% to 13.2% (1). Between 2007 and 2018, the percentage of U.S. adults with diagnosed diabetes achieving treatment goals of glycated hemoglobin <7%, blood pressure <140/90 mmHg, and non-HDL-cholesterol <130 mg/dl decreased from 24.9% to 22.2% (2). And while the age-adjusted incidence of non-traumatic lower extremity amputations in adults with diabetes decreased steadily from 2000 to 2009, the incidence increased progressively after 2010 (3). Recognition of these gaps between what is and what could be led the National Clinical Care Commission (NCCC) to rethink population-wide approaches to the prevention and control of diabetes in the United States.

Methods

In 2017, the United States Congress passed Public Law 115-80 which established the NCCC. The NCCC was charged with evaluating and making recommendations to the Secretary of Health and Human Services and to Congress regarding improving the coordination and leveraging of programs within the Department of Health and Human Services and other federal agencies related to awareness, prevention, and clinical care for diabetes (4). The NCCC included 23 members. Twelve non-federal members represented physician specialists, primary care physicians, health care providers serving Medicaid and uninsured populations, non-physician health care professionals, patient advocates, and public health experts. Eleven additional members each represented a different federal agency. The NCCC systematically collected information on federal policies and programs relevant to diabetes from both health-related and non-health-related federal agencies. It adopted a framework for its deliberations that combined elements of both the Socioecological Model (5) and the Chronic Care Model (6) and recognized that lack of progress in the prevention and control of diabetes is due to a failure to recognize diabetes as both a societal problem and a complex medical problem. It concluded that to prevent and control diabetes, public policies and programs must be aligned to address both social determinants of health and health care delivery as they impact diabetes (4). The authors of this article were as appointed non-federal members of the NCCC.

To develop evidence-based and actionable recommendations, the NCCC formed three subcommittees focused on 1) population-wide strategies to prevent and control diabetes; 2) targeted diabetes prevention strategies for individuals at risk for type 2 diabetes, including those with prediabetes; and 3) the treatment of diabetes and its complications in individuals with diabetes. In this article, we discuss the findings and recommendations of the NCCC's General Populations Sub-Committee as they relate to the social and environmental factors that influence both the risk of type 2 diabetes and the management of type 1 and type 2 diabetes. We argue that population-wide interventions to address social and environmental determinants of health are fundamental to diabetes prevention and control in the U.S (7, 8). Other papers have described the recommendations of the two other sub-committees (9, 10).

Rationale

Americans who have less education, lower incomes, less wealth, food and housing insecurity, and who live in rural areas have higher rates of type 2 diabetes. Rates of type 2 diabetes are higher in neighborhood environments that lack playgrounds, parks, and walkability and in areas where people are exposed to environmental toxins. Poor social cohesion, marginalization, historical trauma, and structural racism also contribute to the diabetes epidemic by increasing exposure to unhealthy environments and conditions (11).

Lower income individuals and racial and ethnic groups that experience higher diabetes prevalence also have higher rates of preventable, severe, and costly complications. Social and environmental factors are associated with self-management of diabetes and improvements in diabetes outcomes have not been evenly distributed across the United States population (12). Poor glycemic control and poor blood pressure control are both more frequent among poor and uninsured people with diabetes than among wealthier and insured people with diabetes (13). Compared to adults with higher incomes, U.S. adults with lower incomes report skipping 23% more doctor visits, tests, treatments, or prescription medications because of cost (14). Non-adherence to medical care due to cost has been reported in 20% to 40% of people with diabetes. For those with self-reported financial insecurity, the non-adherence rate can be as high as 60% (15).

Recently, there has been increasing recognition that social and environmental factors influence health. A recent White House conference on Hunger, Nutrition and Health endorsed medically tailored meals as a first step in addressing food insecurity and nutritional quality as social determinants of health (16). The "food as medicine" concept had its roots in the AIDS epidemic when volunteers delivered meals to patients to prevent the cachexia that individuals with AIDS experienced. In the past few years, the concept of "food as medicine" has been popularized by Medicare Advantage plans that include some variation of home-delivered meals to meet the needs of patients with conditions as diverse as diabetes, kidney disease, and heart failure. A number of states have also offered medically tailored meals through Medicaid under wavers from the Department of Health and Human Services. In one study of over 1,000 adults, weekly delivery of ten ready-to-eat meals tailored to the specific medical needs of the individual under the supervision of a registered dietitian was associated with significantly fewer inpatient admissions, fewer skilled nursing facility admissions, and lower costs (17).

Although medically tailored meals provided by health systems can address food insecurity as a contributor to diabetes and its complications, they are limited in their scope and tend to "medicalize" what is in fact a social issue. Non-health-related federal departments and agencies are responsible for policies and programs that impact food, education, housing, transportation, trade, commerce and the environment, and have an enormous

role in shaping social and environmental conditions that influence population health. The NCCC recognized that implementing changes in the policies and programs of these non-health-related federal agencies and ensuring their cooperation and collaboration with federal agencies that are accountable for health care concerns offers the greatest promise in addressing diabetes in the United States.

While some countries have affirmatively addressed diabetes through trans-sectoral governmental activities, the U.S. has not (18). The U.S. generally lacks structures to coordinate strategic planning across non-health-related and health-related federal agencies. Indeed, many non-health-related federal agencies may inadvertently implement policies and programs that are antithetical to the missions and objectives of health-related federal agencies. A health-in-all policies (HiAPs) approach can address the complex factors that influence health and equity by articulating and integrating health considerations into policy-making across diverse sectors (19). A HiAPs approach takes into account the health implications of policy decisions, seeks synergies between non-health-related and health-related agencies, and avoids harmful health impacts and health inequities that can unintentionally arise from the policies and practices of non-health-related agencies.

Health impact assessments (HIAs) are tools by which policies and programs may be judged as to their potential effects on the health of populations and the distribution of health across populations (18). HIAs are an evidence-based method to promote the HiAP approach. The NCCC recognized that sustained national efforts to adopt a HiAP approach and to mandate HIAs could do much to address social determinants of health and facilitate the prevention and control of diabetes in the United States. Indeed, the federal government can play a larger role in preventing and controlling diabetes by ensuring that non-health-related federal agencies conduct HIAs and consider their results when implementing policies and programs. A number of examples, taken from the Report of the National Clinical Care Commission, follow (4). In the remainder of this report, we describe recommendations made by the NCCC General Populations Sub-Committee, whose purpose was to identify agency actions that affect health risk in the overall population including those without diabetes, those at risk for diabetes, and those with diabetes (4).

Recommendations

Nutrition, food policy, and clean drinking water

Many policies and programs of the United States Department of Agriculture (USDA) profoundly affect the nutritional status of Americans. In fiscal year 2021, the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) served approximately 6.2 million low-income women, infants, and children each month (20, 21). WIC seeks to ensure that low income pregnant and postpartum women and their children up to age 5 have access to nutritious foods, that women deliver infants with appropriate birth weights, that women receive breastfeeding support, and that their children achieve appropriate BMI percentiles. Unfortunately, enrolling in WIC can be difficult, and the proportion of eligible people who participate in WIC is only 57% (22). Recent improvements to the nutritional content of the WIC package have been shown to be beneficial to population health (23). By updating the technology infrastructure of WIC and increasing participation among eligible women, participants could be enabled to buy and consume more fruits and vegetables and breastfeeding could be promoted as the optimal infant feeding choice (7, 8).

The USDA Supplemental Nutritional Assistance Program (SNAP) provides ~$80 billion per year to address food insecurity and improve access to foods and beverages for approximately 42 million lower-income Americans each year (24). SNAP is a valuable program for reducing food insecurity, but its impacts on diet quality and diabetes risk have not been optimized. For example, in 2016, SNAP households spent approximately $4 billion of SNAP resources to purchase sugar-sweetened beverages (SSBs) (25). By expanding outreach to enable all SNAP-eligible individuals to receive SNAP benefits, increasing the benefit to better reflect the current prices of healthy foods in today's marketplace, providing incentives for the purchase of fruits and vegetables, removing SSBs as an allowable SNAP purchase, and expanding educational efforts to reduce nutrition-related diabetes risks, the USDA could better address the nutritional needs of Americans and contribute to the prevention and control of diabetes (7, 8).

Sugar-sweetened beverages (SSBs) represent the largest single source of added sugar in the American diet (30-40%) and account for 50-90% of the recommended daily limit of added sugars (26). The highest intake of SSBs occurs among adolescents, non-Hispanic Black and Hispanic people, and groups with lower socioeconomic status (27). To address this issue, the USDA should require schools to ban the sale of SSBs in order to receive funding through the National School Lunch and Breakfast Program (see below). At the same time, the Departments of Education and the Environmental Protection Agency (EPA) could collaborate to ensure that free and clean water is accessible on all school campuses. Congress could also enact an excise tax of as little as 1 cent per ounce (about 10% of the price) on the cost of SSBs to reduce consumption. The revenues from the tax could then be used to fund health promotion activities including access to safe drinking water (7, 8). Currently, six U.S. localities levy taxes on SSBs (Albany, Berkley, Oakland, and San Francisco, CA, Boulder, CO, and Seattle, WA). Philadelphia, PA also levies a per-volume soda excise tax on purchases of soft drinks. Evaluation of these taxes and similar taxes imposed in the United Kingdom (U.K.) and Mexico have demonstrated that they are associated with reduced SSB consumption (28–31). A recent evaluation of the health impact of the U.K. tax has shown reductions in obesity among children (32).

The USDA also supports the National School Lunch and Breakfast Program which together serve approximately 30 million children each day (33). The Summer Food Services Program and Seamless Summer Option, federally-funded, state-administered programs that reimburse not-for-profit community organizations to serve free, healthy meals to children and teens in low-income communities during the summer are also supported by the USDA

(34). Providing these programs sufficient financial resources to offer foods that meet nutritional standards and expanding the summer meal programs to serve more of the low-income children served by the National School Lunch and Breakfast Program could help to address childhood obesity and prevent type 2 diabetes in youth, which is a growing clinical and public health problem 7,8].

Recently, the USDA added $40 million to a Farm Bill Program called the Gus Schumacher Nutrition Incentive Program (GusNIP), the fresh fruit and vegetables program, to scale up the use of "produce prescriptions" (PRx). PRx are similar to medically tailored meals but provide fresh produce to at-risk individuals either in boxes or through vouchers or debit-type cards. Unlike medically tailored meals, the health impact of PRx has not been rigorously evaluated, but they represent an important first step in marshalling what are traditionally viewed as "non-health-related federal agencies" to improve population health (35). The USDA Farm Bill ($86 billion per year) (36) can be further harnessed to better prevent and control diabetes and reduce disparities by increasing funding to three programs: the Specialty Crop Block Grant Program that targets the cultivation of fruits, vegetables, and tree nuts; the Specialty Crop Research Initiative that addresses the sustainability of the specialty crop industry; and the Healthy Food Financing Initiative that provides grants and loans to improve access to fresh and healthy foods in low-income settings (7, 8).

Food and beverage labeling and marketing

The Food and Drug Administration (FDA) can also be enlisted to improve the nutritional status of the general population by improving food and beverage labeling and limiting misleading product claims. The general public, especially individuals with lower education and income levels, are frequently misinformed about the nutritional value and health risks of foods and beverages (37). Inaccurate and misleading marketing claims about health benefits (such as "whole grain", "low fat", and "real") make it difficult for individuals to accurately identify health risks and make informed food choices. By requiring clear, direct, and compelling food and beverage labeling – such as traffic light icons –to inform consumers' dietary choices, the FDA can contribute to improving the nutritional status of Americans (38). Such an approach has been implemented and proven to be effective in a number of Latin American countries (39, 40). The Federal Trade Commission, if provided the appropriate authority, can also be used to reduce diabetes risk by restricting commercial advertising and marketing of unhealthy foods and beverages to children under the age of 13 years who are unable to objectively evaluate marketing claims (7, 8, 41).

Promoting breastfeeding

Breastfeeding has been shown to be associated with reduced risk of diabetes among mothers and lower rates of obesity among their offspring (42). Having paid maternity leave for at least 3 months is associated with higher rates, longer duration, and greater intensity of breastfeeding (43). Breast feeding and diabetes prevention can be facilitated by the Department of Labor ensuring that all work sites offer lactation support for breastfeeding mothers. Congress could also enact universal, paid maternity leave for at least 3 months to facilitate persistent breastfeeding (7, 8).

The built and ambient environments

Attributes of the built and ambient environments also influence diabetes risk and management and are directly subject to government policies and programs (44–47). Housing quality and area-level attributes such as walkability, green spaces, physical activity resources, and opportunities for active transport are determinants of type 2 diabetes risk (48, 49). The Department of Housing and Urban Development (HUD) and the Internal Revenue Service (IRS), through its Low-income Housing Tax Credit Program, can impact the availability and quality of housing for low-income individuals and families and can expand housing opportunities in low-poverty neighborhoods. The landmark Moving to Opportunity Study demonstrated that moving from a neighborhood with a high level of poverty to one with a lower level of poverty was associated with reductions in the incidence of both extreme obesity and diabetes (50). Similarly, the Department of Transportation can implement policies to enhance green spaces, walkability, and opportunities for active transport. The EPA can also ensure that its policies, practices, regulations, and funding decisions lead to environmental changes to prevent and control exposures to air pollution, contaminated water, and endocrine disrupting chemicals that affect diabetes risk (7, 8, 47, 51, 52).

Coordinating the policies and programs of non-health-related and health-related federal agencies

Finally, there is a need to coordinate and monitor federal efforts to prevent and control diabetes and to ensure trans-agency collaboration among non-health-related and health-related federal agencies. Coordinating the activities of large, non-health-related federal agencies as diverse as USDA, FDA, FTC, the Department of Labor, HUD, IRS, DOT, and EPA with those of health-related federal agencies will be an enormous challenge. An Office of National Diabetes Policy, analogous to the Office of National AIDS Policy, should be created and given responsibility to develop and implement a national diabetes strategy (53, 54).

Conclusions

While much remains to be done to address diabetes as the complex medical problem that it is, a new kind of work must begin to address the social and environmental factors that influence the risk of type 2 diabetes and impact the management of type 1 and type 2 diabetes. As we have indicated in this report, non-health-related federal departments and agencies are responsible for policies and programs that impact food and agriculture, education, housing,

transportation, trade, commerce, and the environment. They play an enormous role in shaping the social and environmental conditions that influence population health. The challenge before us is to implement changes in the policies and programs of these so-called "non-health-related" federal agencies, to enable their cooperation and collaboration with agencies that are accountable for health care concerns, and to ensure that their policies are aligned to address diabetes and its complications in the United States.

Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Author contributions

Both authors contributed to the study conception and design. The first draft of the manuscript was written by WHH. Both authors edited, read, and approved the final manuscript.

Funding

WHH was supported, in part, by National Institutes of Health grant P30 DK092926. DS was supported, in part, by National Institutes of Health grant 2P30 DK092924 and CDC grant U18DP006526.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Both WHH and DS were appointed, non-federal members of the National Clinical Care Commission.

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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 26 June 2023
DOI 10.3389/fendo.2023.1188784

OPEN ACCESS

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RECEIVED 17 March 2023
ACCEPTED 02 June 2023
PUBLISHED 26 June 2023

CITATION
Nieto-Martinez R, Barengo NC, Restrepo M, Grinspan A, Assefi A and Mechanick JI (2023) Large scale application of the Finnish diabetes risk score in Latin American and Caribbean populations: a descriptive study. *Front. Endocrinol.* 14:1188784. doi: 10.3389/fendo.2023.1188784

Large scale application of the Finnish diabetes risk score in Latin American and Caribbean populations: a descriptive study

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Background: The prevalence of type 2 diabetes (T2D) continues to increase in the Americas. Identifying people at risk for T2D is critical to the prevention of T2D complications, especially cardiovascular disease. This study gauges the ability to implement large population-based organized screening campaigns in 19 Latin American and Caribbean countries to detect people at risk for T2D using the Finnish Diabetes Risk Score (FINDRISC).

Methods: This cross-sectional descriptive analysis uses data collected in a sample of men and women 18 years of age or older who completed FINDRISC *via* eHealth during a Guinness World Record attempt campaign between October 25 and November 1, 2021. FINDRISC is a non-invasive screening tool based on age, body mass index, waist circumference, physical activity, daily intake of fruits and vegetables, history of hyperglycemia, history of antihypertensive drug treatment, and family history of T2D, assigning a score ranging from 0 to 26 points. A cut-off point of ≥ 12 points was considered as high risk for T2D.

Results: The final sample size consisted of 29,662 women (63%) and 17,605 men (27%). In total, 35% of subjects were at risk of T2D. The highest frequency rates (FINDRISC ≥ 12) were observed in Chile (39%), Central America (36.4%), and Peru (36.1%). Chile also had the highest proportion of people having a FINDRISC ≥15 points (25%), whereas the lowest was observed in Colombia (11.3%).

Conclusions: FINDRISC can be easily implemented *via* eHealth technology over social networks in Latin American and Caribbean populations to detect people

10.3389/fendo.2023.1188784

with high risk for T2D. Primary healthcare strategies are needed to perform T2D organized screening to deliver early, accessible, culturally sensitive, and sustainable interventions to prevent sequelae of T2D, and reduce the clinical and economic burden of cardiometabolic-based chronic disease.

KEYWORDS

glucose metabolism, epidemiology, diabetes screening, dissemination, diabetes risk assessment

Introduction

The prevalence of type 2 diabetes (T2D) continues to increase in the Americas (1) and worldwide. Recent estimates by the International Diabetes Federation have revealed that 537 million people were living with diabetes in 2021 and this number will most likely increase by 46%, reaching 784 million by 2045 (2). Additionally, all Latin American and Caribbean countries exhibited an increased proportion of all-cause mortality attributable to T2D in the last 30 years (by ~4.7% in men and ~4.8% in women) (3). Arguably, the most troubling aspect of this situation is that many people with T2D are not even aware of their condition; for example, in South and Central America, one out of three patients with diabetes is currently undiagnosed (4). Identification of people with prediabetes or early T2D has been one of the great challenges of modern medicine and reconciling prediabetes as a distinct component of this chronic disease state has been controversial, and at times, even contentious (5) . Though the evidence affirms critical roles of intensive lifestyle change and pharmacotherapy (6–8), large-scale implementation of a formal preventive care approach to mitigating insulin resistance, hyperglycemia, and their respective complications has been elusive.

The dysglycemia-based chronic disease (DBCD) model constitutes a new framework for prevention in the cardiometabolic space. This model comprises 4 stages: stage 1-risk (insulin resistance), stage 2-predisease (prediabetes), stage 3-disease (T2D), and stage 4-complications (vascular disease) (9). The current DBCD model has evolved over the last few years and represents but one of 3 dimensions (i.e., stages, drivers, and social/transcultural determinants), and but one of 5 drivers (the others are abnormal adiposity, hypertension, dyslipidemia, and residual factors such as inflammation) of cardiometabolic-based chronic disease (CMBCD) (10–13). By adopting the DBCD model, a formal culturally adapted, preventive care paradigm can be applied at earlier stages to decrease chronic disease progression and mitigate clinical and economic burdens (9, 14). Pragmatically, insulin resistance and prediabetes are actionable opportunities for early detection to initialize this preventive care process. Fortunately, risk scores have been established as practical and cost-effective tools (15) to identify people at risk for T2D, which could then prompt guideline-directed diagnostic testing, followed by lifestyle change and/or judicious pharmacotherapy/procedures (16, 17).

The Finnish Diabetes Risk Score (FINDRISC) is composed of eight easy-to-collect variables and is the most popular screening tool worldwide (18). The sensitivity and specificity of the FINDRISC to predict 10-year risk of drug-treated T2D are 78-81% and 76-77%, respectively (18). The FINDRISC also identifies patients with abnormal glucose tolerance and occult T2D (19). Of particular importance, the FINDRISC has been applied in several countries and distinct cultures, such as Colombia (20, 21), Venezuela (22), Peru (23), Uruguay (24), Brazil (25), Germany (26), New Zealand (27), U.S (28, 29)., Belgium (30) Spain (31), Greece (32), Jordan (33), Poland (34), Malaysia (35), Turkey (36), Lebanon (25), Norway (37), Sweden (38), Indonesia (39), and aggregated medical practices in Europe (40), leading to the development of population-specific T2D screening. A version of the FINDRISC using specific cutoffs for waist circumference (WC) for the Latino population has also been validated (21, 41) and performs similarly to other FINDRISC versions (23, 42). Most studies describe the accuracy of T2D risk scores for specific populations, but not the implementation logistics in populations at risk (21–23, 29, 41, 43).

Telehealth and social networking have accelerated the implementation of screening tools during the COVID-19 pandemic and can be applied to preventive care plans for chronic metabolic diseases (44). However, relatively few studies have been published on the results of implementing T2D risk scores in large populations (45–49). Even though the FINDRISC has been successfully implemented in several primary healthcare systems (19, 40, 47, 50), this study aims to identify people at high risk of T2D using the FINDRISC through a large population-based telehealth campaign performed in 19 Latin American and Caribbean countries.

Material and methods

Study design and population

This cross-sectional descriptive study included a non-probabilistic sample of men and women 18 years of age or older who agreed to complete the FINDRISC on an eHealth platform exclusively available for the period of data collection. Digital surveys were carried out to comply with a Guinness World Record (GWR)

attempt campaign entitled "Most digital T2D screening forms collected in 1 week" between October 25 and November 1, 2021 (Brasilia time). To obtain auditable results, the study website including terms, conditions, and privacy policies required management by a third-party data manager. To verify that the methodology was fulfilled (i.e., the surveys corresponded to the FINDRISC questionnaire and users only completed the questionnaire once), two external auditors, one from the medical area and the other from the digital area, were required by the GWR campaign.

The campaign was conducted in 19 countries in North America (Mexico), Central America (Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica, Panama, Dominican Republic, Jamaica, Trinidad and Tobago, Bahamas, Barbados, Aruba, and Curaçao), and South America (Colombia, Chile, Ecuador, Brazil, and Peru). In each country, the FINDRISC was disseminated through press releases and social networks (Instagram® and Facebook®). In some countries, influencers made the link to the website known to their followers. Others interested in participating received the website link to complete the FINDRISC. Once entering the website, participants selected the country of residence, accepted the terms and conditions, and registered their name, last name, and e-mail. User data was protected by confidentiality terms. The data manager performed the database cleaning, eliminating repetitions and inconsistencies. Surveys in which the user did not accept the terms and conditions, did not answer all the questions, or made multiple entries were excluded. The social media channel proviuded constant metrics regarding the usage of the questionnaire through google and meta-analytics. The Guinness records organization demanded an independent platform to manage the metrics for this record attempt. That platform was specifically designed to pull the data from google and meta-analytics, so we did not have any influence in its results during the week the screening campaign was performed. Furthermore, the screening platform was managed by an independent agency.

Assessing type 2 diabetes risk

The FINRISC is a non-invasive tool that assigns a score from 0 to 26 points to estimate the T2D risk. FINDRISC was translated into Spanish (www.unrecordporlasalud.com), Portuguese (www.umrecordepelasaude.com), and English (www.arecordforheatlh.com). FINDRISC variable definitions and categories are summarized in Table 1.

Selection of the FINDRISC cutoffs

The results of studies using, validating, and adapting the FINDRISC in Latin America to identify people with unknown T2D or at risk for T2D (prediabetes: impaired fasting glucose and/or impaired glucose tolerance) is given in Table 2. Most studies used the Latin American FINDRISC (LA-FINDRISC), a modified version that applied specific WC cutoffs for the Latino population and compared them with the original FINDRISC (21, 22, 24, 41). The cut-off level used when applying the LA-FINDRISC (21) or a modified FINDRISC (20) to identify people with previously unknown T2D within the clinical setting was 14 points. However, thresholds as low as 10 points were applied in some studies that used the FINDRISC to screen the general population for undetected T2D (21, 22). A cut-off point of ≥ 12

TABLE 1 Categorization and definitions of FINDRISC components.

FINDRISC T2D risk categories[1]	Score	Risk[2] (%)
Low	0-6	1
Mild	7-11	4
Middle	12-14	17
High	15-20	33
Very high	21-26	50
FINDRISC variables	Variable categories	Score[1]
Age	<45	0
	≥ 45 to < 55	2
	≥ 55 to < 65	3
	≥ 65	4
BMI (kg/m^2)	Normal (<25)	0
	Overweight (≥ 25 to < 30)	1
	Obesity (≥ 30)	3
WC (cm)	Normal (Men, < 94; women, < 80)	0
	Moderately high WC (Men, ≥ 94 to < 102; women, ≥ 80 to < 88)	3
	Abdominal obesity (Men, ≥ 102, women ≥ 88)	4
≥ 30 min of physical activity/day	No	0
	Yes	2
Daily vegetables/fruits intake	No	0
	Yes	1
Use of blood pressure medication	No	0
	Yes	2
History of high blood glucose	No	0
	Yes	5
Family history of diabetes	No	0
	Yes (second degree relatives[3])	3
	Yes (first degree relatives[4])	5
Maximum total score		26

[1]Data from the original FINDRISC study (18). [2]Risk to develop T2D in the next 10 years. [3]Second degree relatives include grandparents, aunt, uncle or first cousin. [4]First degree relatives include parents, brother, sister, or own child.
BMI, Body mass index; FINDRISC, Finnish Diabetes Risk Score; T2D, type 2 diabetes; WC, waist circumference.

TABLE 2 Validation of FINDRISC in Latin America to identify people with previously unknown prediabetes and type 2 diabetes.

Risk Score	Country / Year	Author / Reference	Population setting	n	Diagnostic test	Aim	Sensitivity/ Specificity (%)	AUC-ROC	Cut-off to detect IGT or uT2D
Original FINDRISC	Finland/ 2003	Lindstrom and Tuomilehto (7, 18)	General population	4,435	OGTT	Determine if T2D can be prevented by lifestyle interventions in subjects at high risk for the disease	O-FINDRISC Cohort (1987) 78/81 Cohort (1992) 77/76	O-FINDRISC Cohort (1987) 0.85 Cohort (1992) 0.87	≥ 9
LA-FINDRISC	Colombia/ 2012	Aschner et al (41)	General population	421	OGTT	Compare LA-FINDRISC vs O-FINDRISC	LA-FINDRISC Men 74/60 Women 77/67	LA-FINDRISC Men 0.77 Women 0.78	> 12
	Venezuela/ 2012	Aschner et al (41)	Clinical	334	OGTT	Compare LA-FINDRISC vs O-FINDRISC	LA-FINDRISC Men 97/70 Women 91/78	LA-FINDRISC Men 0.91 Women: 0.92	> 14
	Uruguay/ 2015	Vignoli et al (24)	Clinical	109	OGTT	Evaluate LA-FINDRISC performance	LA-FINDRISC 70/66	LA-FINDRISC Overall 0.74	> 14
	Venezuela/ 2015	Nieto-Martínez et al. (22)	General population (National)	3,061	OGTT	Compare LA-FINDRISC vs O-FINDRISC	LA-FINDRISC For uT2D: Men 72/ 62; Women 71/65 For IGT: Men 65/63 Women 64/62	LA-FINDRISC For uT2D: Men 0.72 Women 0.72 For IGT: Men 0.69 Women 0.67	For uT2D ≥ 9 men ≥ 10 women For IGT ≥ 9 (both sexes)
ColDRISC*	Colombia/ 2015	Barengo et al. (51)	Captive population (insurance company)	2,060	OGTT	Develop and compare ColDRISC vs LA-FINDRISC	ColDRISC 73/67 LA-FINDRISC 72/60	ColDRISC 0.74 LA-FINDRISC 0.73	ColDRISC > 4
Modified FINDRISC	Colombia/ 2015	Gomez-Arbelaez et al. (20)	Clinical	772	A1C	To evaluate the performance of FINDRISC detecting and predicting T2D	Modified-FINDRISC Men 66/75 Women 71/62	Modified-FINDRISC Men 0.74 Women 0.71	> 14
Peruvian "simplified" Risk Score*	Peru/2018	Bernabe-Ortiz et al (23)	General population	1,609	OGTT	Compare O-FINDRISC, LA-FINDRISC, and Peruvian Risk Score, and derived Simplified FINDRISC version		O-FINDRISC 0.69, LA-FINDRISC 0.68 Peruvian Risk Score 0.64 Simplified FINDRISC 0.71	

A1C, Glycated hemoglobin A1C; AUC, area under the curve; IFG, impaired fasting blood glucose; IGR, Impaired glucose regulation;, IGT, impaired glucose tolerance; O-FINDRISC, Original Finnish Diabetes Risk Score; OGTT, Oral glucose tolerance test; ROC, receiver-operating characteristic; T2D, type 2 diabetes; uT2D, unknown type 2 diabetes. FINDRISC versions: (1) ColDRISC: Colombian Diabetes Risk Score, (2) LA-FINDRISC: Latin America FINDRISC, (3) Modified FINDRISC: include a modification in the WC cut-off values: Men: < 90 cm (0 risk points); 90-98 cm (3 risk points); > 98 cm (4 risk points). Women: < 80 cm, (0 risk points); 80-88 cm (3 risk points); > 88 cm (4 risk points). *Score is not comparable with the O-FINDRISC version.

points was considered as being at high risk of T2D and therefore needing diagnostics tests. This threshold was a consensual cutoff recommended in most Latin American countries.

Statistical analysis

Data were analyzed using SPSS 20 software (IBM corp. Released 2011; Armonk, NY, USA). Frequencies were presented as percentages and 95% confidence intervals (CI), and differences between groups were considered when no 95% CI overlap was detected. A p-value of <0.05 was considered statistically significant. All procedures were performed in accordance with the Helsinki Declaration. This study was considered as Non-Human Subject Research and therefore not requiring Institutional Review Board approval.

Results

Subjects' characteristics

The final sample size comprised 47,267 subjects from 19 countries, comprising 13 Central American countries (merged for the analysis and reported as the Central America region), Mexico, Colombia, Chile, Ecuador, Brazil, and Peru. Of the total sample,

10.3389/fendo.2023.1188784

62.8% were women with a mean age of 48 ± 0.02 (mean ± SE), 86.8% were < 55 years of age, and 89.4% were from Brazil, Mexico, or Peru. Compared with the women, the men were older (+ 9% of subjects ≥ 45 years), with a higher proportion of overweight (+ 11.9%), less daily intake of fruits and vegetables (-1.8%), and greater use of blood pressure medications (+7.1%). Compared with the men, the women had a higher proportion of abdominal obesity (+ 9.5%), physical inactivity (+ 12.3%), personal history of high blood glucose (+ 1.1%), and second-degree relatives with a history of T2D (+ 4.6%) (Table 3).

FINDRISC components by T2D risk categories

Overall, 33% the subjects were at low risk to develop T2D (FINDRISC < 7), 32.3% at slightly elevated risk (FINDRISC 7-11), 16.2% at moderate risk (FINDRISC 12-14), 15.5% at high risk (FINDRISC 15-20), and 3.0% at very high risk (FINDRISC > 20) (Table 4). The risk of T2D increased with age, adiposity, physical inactivity, low intake of fruits and vegetables, use of blood pressure medications, history of hyperglycemia, and family history of T2D. Although 42.9% of the youngest population (< 45 years of age) had a low risk (FINDRISC < 7), 9.9% of them had a high risk of T2D (FINDRISC 15-20). The proportion of subjects at high risk of T2D increased in each decade of age reaching 34.0% in those ≥ 65 years old.

The risk of T2D was low or slightly elevated (FINDRISC < 12) in 89.1% of subjects with normal weight and 90% of subjects without abdominal obesity. Excess total (by BMI) and central (by WC) adiposity increased the risk of T2D. Compared with subjects with normal weight (3.6%), the high risk of T2D (FINDRISC 15-20) increased to 13.9% in subjects with overweight and 34.2% in those with obesity, and the proportion of subjects with very high risk (FINDRISC > 20) increased 5-fold with overweight and almost 30-fold with obesity. Compared with normal WC (3.0%), a high risk of T2D (FINDRISC 15-20) increased to 20.8% in subjects with moderately-high WC and to 39.0% in those with abdominal obesity, and the proportion of subjects with very high risk (FINDRISC > 20) increased 16 times with a moderate increase in WC and almost 50 times with the presence of abdominal obesity (Table 4).

Almost 80% of subjects with a FINDRISC < 12 reported participating in ≥ 30 min of physical activity/day compared to less than 1% in the very high-risk group (score > 20). Likewise, 70% of those with low-mild risk of T2D reported that they consumed fruits and vegetables daily compared to only 2.6% in the very high-risk group. Sixty-eight percent of subjects with FINDRISC ≥ 12 reported using blood pressure medication. In the T2D high risk and

TABLE 3 Characteristics of study subjects by sex.

	Total	Men	Women
	n (%, 95%CI)	n (%, 95%CI)	n (%, 95%CI)
Total	47267	17605 (37.2, 36.8 - 37.7)	29662 (62.8, 62.3 - 63.2)
Countries			
Brazil	21925 (46.4, 45.9-46.8)	8899 (50.5, 49.8 - 51.3)	13026 (43.9, 43.4 - 44.5)
Mexico	15264 (32.3, 31.9-32.7)	5823 (33.1, 32.4 - 33.8)	9441 (31.8, 31.3 - 32.4)
Peru	5059 (10.7, 10.4-11.0)	1049 (6.0, 5.6 - 6.3)	4010 (13.5, 13.1 - 13.9)
Colombia	2331 (4.9, 4.7-5.1)	912 (5.2, 4.9 - 5.5)	1419 (4.8, 4.5 - 5.0)
Central America	1117 (2.4, 2.2-2.5)	434 (2.5, 2.2 - 2.7)	683 (2.3, 2.1 - 2.5)
Ecuador	663 (1.4, 1.3-1.5)	234 (1.3, 1.2 - 1.5)	429 (1.4, 1.3 - 1.6)
Chile	520 (1.1, 1.0-1.2)	171 (1.0, 0.8 - 1.1)	349 (1.2, 1.1 - 1.3)
	% (95% CI)	% (95% CI)	% (95% CI)
Age (years)			
<45	66.7 (66.3-67.1)	61.1 (60.4-61.8)	70.0 (69.5-70.5)
≥ 45 to < 55	20.1 (19.7-20.4)	22.7 (22.1-23.3)	18.5 (18.0-18.9)
≥ 55 to < 65	9.9 (9.7-10.2)	12.1 (11.6-12.6)	8.6 (8.3-8.9)
≥ 65	3.3 (3.2-3.5)	4.1 (3.8-4.4)	2.9 (2.7-3.1)
BMI (kg/m^2)			
Normal weight (<25)	36.4 (35.9-36.8)	28.5 (27.9-29.2)	41.0 (40.5-41.6)

(Continued)

TABLE 3 Continued

	Total	Men	Women
	n (%, 95%CI)	n (%, 95%CI)	n (%, 95%CI)
Overweight (≥ 25 to < 30)	37.2 (36.7-37.6)	44.6 (43.9-45.4)	32.7 (32.2-33.3)
Obesity (≥ 30)	26.4 (26.1-26.9)	26.9 (26.2-27.5)	26.3 (25.8-26.8)
WC (cm)			
Normal (Men, < 94; women, < 80)	48.8 (48.4-49.3)	52.2 (51.5-53.0)	46.8 (46.2-47.3)
Moderately high WC (Men, ≥ 94 to < 102; women, ≥ 80 to < 88)	32.4 (32.0-32.8)	35.0 (34.3-35.7)	30.9 (30.4-31.4)
Abdominal obesity (Men, ≥ 102, women ≥ 88)	18.8 (18.4-19.1)	12.8 (12.3-13.3)	22.3 (21.9-22.8)
≥ 30 min of physical activity/day (no)	57.3 (56.9-57.8)	49.6 (48.9-50.4)	61.9 (61.3-62.4)
Daily vegetables/fruits intake (no)	40.8 (40.3-41.2)	41.9 (41.2-42.7)	40.1 (39.5-40.7)
Use of blood pressure medication (yes)	18.9 (18.5-19.2)	23.3 (22.7-23.9)	16.2 (15.8-16.7)
History of high blood glucose (yes)	22.5 (22.1-22.9)	21.8 (21.2-22.4)	22.9 (22.4-23.4)
Family history of diabetes			
No	30.0 (29.6-30.4)	33.3 (32.7-34.0)	28.0 (27.5-28.5)
Second degree relatives[1] (yes)	39.0 (38.6-39.5)	36.1 (35.4-36.8)	40.7 (40.2-41.3)
First degree relatives[2] (yes)	31.0 (30.6-31.4)	30.6 (29.8-31.2)	31.3 (30.7-31.8)
FINDRISC score ≥ 12	34.7 (34.3-35.2)	33.7 (33.0-34.4)	35.4 (34.8-35.9)
FINDRISC score ≥ 15	18.5 (18.2-18.9)	18.3 (17.8-18.9)	18.7 (18.2-19.1)

Frequencies are expressed as percentages and 95% CI and differences were considered when no 95% CI overlap was detected. [1]Second degree relatives include grandparents, aunt, uncle or first cousin. [2]First degree relatives include parents, brother, sister, or own child.
BMI, Body mass index; CI, Confidence Interval; FINDRISC, Finnish Diabetes Risk Score; WC, Waist circumference.

TABLE 4 Distribution of FINDRISC components by T2D risk categories.

FINDRISC categories Risk to develop T2D in the next 10 years	< 7 Low (1%)	7-11 Mild (4%)	12-14 Middle (17%)	15-20 High (33%)	>20 Very high (50%)
Total (%, 95%CI)	33.0 (32.6 - 33.4)	32.3 (31.9 - 32.7)	16.2 (15.8 - 16.5)	15.5 (15.2 - 15.9)	3.0 (2.8 - 3.2)
Age (years)					
<45	42.9 (42.4 - 43.5)	32.7 (32.2 - 33.2)	13.8 (13.4 - 14.1)	9.9 (9.5 - 10.2)	0.7 (0.6 - 0.8)
≥ 45 to < 55	15.3 (14.6 - 16.1)	34.3 (33.4 - 35.3)	21.2 (20.4 - 22.0)	23.6 (22.8 - 24.5)	5.6 (5.1 - 6.0)
≥ 55 to < 65	10.3 (9.5 - 11.2)	27.9 (26.7 - 29.2)	20.8 (19.7 - 22.0)	31.3 (29.9 - 32.5)	9.7 (8.9 - 10.6)
≥ 65	6.9 (5.7 - 8.2)	24.3 (22.3 - 26.5)	20.8 (18.8 - 22.8)	34.0 (31.8 - 36.5)	14.0 (12.3 - 15.8)
BMI (kg/m^2)					
Normal (<25)	60.2 (59.4 - 60.9)	28.9 (28.2 - 29.6)	7.0 (6.7 - 7.4)	3.6 (3.4 - 3.9)	0.3 (0.2 - 0.4)
Overweight (≥ 25 to < 30)	26.6 (25.9 - 27.2)	41.0 (40.2 - 41.7)	17.0 (16.5 - 17.6)	13.9 (13.4 - 14.5)	1.5 (1.3 - 1.7)
Obese (≥ 30)	4.7 (4.3 - 5.1)	24.8 (24.0 - 25.5)	27.5 (26.8 - 28.3)	34.2 (33.4 - 35.0)	8.8 (8.3 - 9.3)
WC (cm)					
Normal (Men, < 94; women, < 80)	60.3 (59.7 - 60.9)	29.7 (29.1 - 30.3)	6.8 (6.4 - 7.1)	3.0 (2.8 - 3.3)	0.2 (0.2 - 0.3)
Moderately high WC (Men, ≥ 94 to < 102; women, ≥ 80 to < 88)	10.2 (9.8 - 10.7)	41.8 (41.0 - 42.6)	24.0 (23.3 - 24.7)	20.8 (20.1 - 21.4)	3.2 (3.0 - 3.5)

(Continued)

TABLE 4 Continued

FINDRISC categories Risk to develop T2D in the next 10 years	< 7 Low (1%)	7-11 Mild (4%)	12-14 Middle (17%)	15-20 High (33%)	>20 Very high (50%)
Abdominal obesity (Men, ≥ 102, women ≥ 88)	1.3 (1.1 - 1.5)	22.7 (21.8 - 23.5)	27.2 (26.3 - 28.2)	39.0 (38.0 - 40.1)	9.8 (9.2 - 10.4)
≥ 30 min of physical activity/day					
No	21.8 (21.3 - 22.3)	33.7 (33.2 - 34.3)	19.5 (19.0 - 20.0)	20.4 (19.9 - 20.9)	4.6 (4.4 - 4.9)
Yes	48.1 (47.3 - 48.7)	30.4 (29.7 - 31.0)	11.7 (11.3 - 12.2)	9.0 (8.7 - 9.4)	0.8 (0.7 - 1.0)
Daily vegetables/fruits intake					
No	24.7 (24.1 - 25.3)	33.7 (33.0 - 34.3)	18.8 (18.3 - 19.4)	19.2 (18.6 - 19.7)	3.6 (3.3 - 3.9)
Yes	38.7 (38.1 - 39.3)	31.3 (30.8 - 31.9)	14.3 (13.9 - 14.7)	13.1 (12.7 - 13.5)	2.6 (2.4 - 2.8)
Use of blood pressure medication					
No	39.0 (38.5 - 39.5)	34.0 (33.6 - 34.5)	15.1 (14.7 - 15.4)	11.0 (10.7 - 11.3)	0.9 (0.8 - 1.0)
Yes	7.0 (6.5 - 7.6)	24.8 (23.9 - 25.7)	21.0 (20.2 - 21.9)	35.2 (34.2 - 36.1)	12.0 (11.3 - 12.7)
History of high blood glucose					
No	42.0 (41.5 - 42.6)	36.3 (35.8 - 36.8)	14.7 (14.3 - 15.0)	6.8 (6.5 - 7.0)	0.2 (0.2 - 0.3)
Yes	1.7 (1.5 - 2.0)	18.6 (17.9 - 19.4)	21.3 (20.6 - 22.1)	45.8 (44.9 - 46.8)	12.6 (11.9 - 13.2)
Family history of diabetes					
No	57.5 (56.7 - 58.3)	29.8 (29.0 - 30.5)	7.7 (7.3 - 8.1)	4.8 (4.5 - 5.2)	0.2 (0.1 - 0.3)
Second degree relatives[1] (yes)	33.9 (33.3 - 34.6)	34.5 (33.8 - 35.2)	17.1 (16.6 - 17.6)	13.0 (12.6 - 13.5)	1.5 (1.3 - 1.6)
First degree relatives[2] (yes)	8.1 (7.6 - 8.5)	32.0 (31.2 - 32.7)	23.2 (22.6 - 23.9)	29.1 (28.4 - 29.8)	7.6 (7.2 - 8.1)

Frequencies are expressed as percentages and 95% CI and differences were considered when no 95% CI overlap was detected. [1]Second degree relatives include grandparents, aunt, uncle or first cousin. [2]First degree relatives include parents, brother, sister, or own child.
BMI, Body mass index; CI, Confidence Interval; FINDRISC, Finnish Diabetes Risk Score; T2D, type 2 diabetes; WC, waist circumference.

very-high risk groups, the use of BP medication was 3 and 13 times higher, respectively. A personal history of hyperglycemia was reported by 80% of subjects with a FINDRISC ≥ 12. In the groups with high and very-high risk for T2D, a history of hyperglycemia was 7 and 63 times higher, respectively. Sixty percent and 31.6% of subjects with a FINDRISC ≥ 12 reported first and second-degree relatives with T2D, respectively, whereas only 12.7% did not (Table 4).

T2D risk in different countries/regions

In total, 34.5% and 18.5% of all study subjects reported a FINDRISC of at least 12 points and 15 points respectively (Table 3; Figure 1), which provides an approximate number of people at risk of T2D in the countries surveyed. No differences by sex were found (Table 3). Using a cutoff of ≥ 12 points, the risk of T2D was similar in all studied countries varying from 34.4% in Ecuador to 39% in Chile, but lowest in Colombia (22.7%) than the rest of the countries. Using a cutoff of ≥ 15 points, the risk of T2D was similar in all countries ranging from 16.9% in Ecuador to 19.9% in Brazil, but lowest in Colombia (11.4%) and highest in Chile (25%), compared with the rest of the countries (Figure 1).

More than 80% of subjects were under 55 years of age. The youngest population was in Peru (96% < 55 y), whereas the oldest were in Brazil (18.0% ≥ 55 y). The prevalence of obesity was highest in Central America (37.7%), and lowest in Colombia (15.1%). Abdominal obesity was most prevalent in Peru (30.6%) and least prevalent in Colombia (10.2%). Reporting at least 30 minutes of physical activity was highest in Colombia (51.8%) and lowest in Peru (30.7%); whereas daily intake of fruits and vegetables was most prevalent in Brazil (66.1%) and least prevalent in Peru (37.7 %) The use of blood pressure medications was similar in all countries (ranging from 17.9% in Mexico to 21.4% in Brazil), except in Peru where it was lowest (9.9%). A personal history of hyperglycemia ranged from 20.1% in Mexico to 33.1% in Chile. A family history of T2D in first degree relatives was highest in Mexico (36.7%) and lowest in Colombia (18.7%) (Table 5).

Discussion

Large-scale application of the FINDRISC eHealth version as part of an organized screening program to assess risk for T2D was feasible in Latin American and Caribbean populations representing 19 countries. The 47,267 subjects evaluated in 1 week set a Guinness

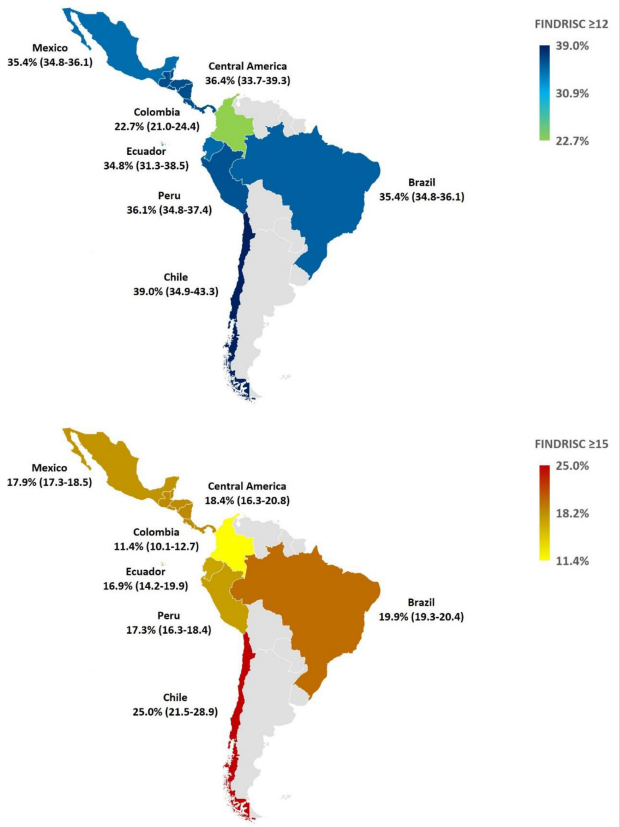

FIGURE 1
Geographical map of FINDRISC scores ≥12 points (upper) and ≥15 points (bottom) by country/region. Frequencies are expressed as percentages and 95% CI ≥12 points (upper) and ≥15 points (bottom) by country. Differences were considered when no 95% CI overlap was detected. Data from Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica, Panama, Dominican Republic, Jamaica, Trinidad and Tobago, Bahamas, Barbados, Aruba, and Curaçao were aggregated as Central America region. CI, Confidence Interval; FINDRISC, Finnish Diabetes Risk Score.

World Record. This study revealed that 35% of the population studied was at risk of T2D, with 1,418 (3%) having a 50% risk for developing T2D in the next 10 years. In this very high-risk group, the risk increased with low fruit and vegetable intake by 1.4 times, low physical activity by 6 times, use of blood pressure medications by 13 times, age > 65 years by 20 times, obesity by 29 times, family history of T2D by 38 times, abdominal obesity by 49 times, and history of hyperglycemia by 63 times.

Applications of FINDRISC scoring in Latin America incorporate specific cut-offs to detect prediabetes, occult T2D, or known T2D (20–24, 41, 42), but few have been leveraged to proactively detect subjects at risk of T2D with the intent of initializing a formal preventive care plan. Diagnostic and prognostic models for T2D among randomly selected adults in Latin America are also scarce (43). Community pharmacy-based opportunistic screening programs are one such example of successful implementation of FINDRISC scoring. In one campaign spanning 854 pharmacies from Spain and Italy, FINDRISCs were collected in 7,234 subjects (52). Of them, 65.5% (vs 65.3% in this study) were at low/slightly elevated risk to develop T2D (FINDRISC < 12), 19.3% (vs 16.2% in this study) were at moderate risk (FINDRISC 12-14), 13.9% (vs 15.5% in this study) were at high risk (FINDRISC 15-20), and 1.4% (vs 3.0% in this study) were at very high risk (FINDRISC > 20). Subjects showing a higher risk of T2D (FINDRISC ≥ 15) in Spain (16.7%) and Italy (14.7%) were lower than Chile (25%), Brazil (19.9%), Central America (18.4%), Mexico (17.9%), Peru (17.3%), and Ecuador (16.9%) in this study, but higher than Colombia (11.4%) (52). A similar campaign performed in 345 municipalities in Brazil involving 977 pharmacists and testing 17,580 subjects between 20 and 79 years found that 22.7% had a high/very high risk of T2D (FINDRISC ≥ 15) (53). This finding is higher than that in the present study in Brazil (19.9%), consistent with a higher risk profile among pharmacy customers compared with eHealth subjects. This is affirmed by an Italian study, in which one-year follow-up after FINDRISC screening of 5,977 community pharmacy customers found that compared with the total sample, those with a FINDRISC ≥ 12 (53% of the total sample) had more fasting blood glucose (FBG; 53.5 vs. 47.8%) and A1C (17.6 vs 12.1%) measurements, as well as evaluations by diabetologists (6.7% vs 5.2%) (54).

Large-scale organized or opportunistic screening to detect patients at risk for T2D should be followed by aggressive case finding, diagnostic testing, lifestyle interventions, and if indicated, pharmaceutical treatment. Using FINDRISC for opportunistic initial screening in 1,377 subjects in Italy followed by FBG measurement in those with a FINDRISC ≥ 9 and then OGTT in those with FBG 100-125 mg/dl, identified 57% with IGT and 83% of cases of T2D (47). Data from 3,866 NHANES subjects showed that the combination of FINDRISC and A1C, compared to FINDRISC alone, improved the sensitivity for detecting T2D from 79.1% to 84.2%, while maintaining similar specificity (48.6% vs 48.3%) (28). In Argentina, combining both organized and opportunistic recruitment, 3,759 individuals completed the FINDRISC, with 43% scoring ≥ 13 points (cutoff selected by expert opinion). This high-risk group then underwent OGTT, detecting 47% with prediabetes (49). A pooled sensitivity and specificity analysis of T2D diagnosis showed that using an A1C-based definition alone will not identify a substantial proportion of previously undiagnosed people who would be considered as having T2D using a glucose-based test; 47.2% less vs FBG, 62.8% less vs OGTT, and 69.6% less vs FBG or OGTT (55). Although the use of A1C for everyone in the T2D care process and creation of infrastructure with this aim has been recommended in various Latin American countries (56), not all laboratories where A1C is measured are properly certified and OGTT could be more accessible and affordable than A1C.

This study elucidates the asymmetric distribution of T2D risk factors among Latin American and Caribbean countries, which has direct impact on public health initiatives such as organized screening, diagnostic testing, and preventive care plans. Except for older subjects in Brazil, younger ones in Peru, and those with a family history of T2D in Mexico, non-modifiable risk factors (i.e., age and family history of T2D) were similar among the countries studied. This indicates that a large part of T2D risk derives from modifiable factors (e.g., adiposity, dysglycemia, hypertension, and eating patterns) that are potentially mitigated by healthy lifestyle

10.3389/fendo.2023.1188784

TABLE 5 Distribution of T2D risk and FINDRISC components by studied countries/region.[1].

	Chile	Brazil	Central America *	Mexico	Peru	Ecuador	Colombia
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
FINDRISC categories							
< 7 (Low risk)	30.2 (26.4 - 34.3)	33.3 (32.7 - 33.9)	30.7 (28.1 - 33.5)	32.5 (31.7 - 33.2)	28.7 (27.5 - 30.0)	32.4 (29.0 - 36.1)	45.2 (43.2 - 47.2)
7-11 (Mild risk)	30.8 (27.0 - 34.9)	31.3 (30.7 - 31.9)	32.9 (30.2 - 35.7)	32.9 (32.2 - 33.6)	35.2 (33.9 - 36.5)	32.7 (29.3 - 36.4)	32.2 (30.3 - 34.1)
12-14 (Middle risk)	14.0 (11.3 - 17.3)	15.6 (15.1 - 16.1)	18.0 (15.9 - 20.4)	16.7 (16.1 - 17.3)	18.8 (17.7 - 19.9)	17.9 (15.2 - 21.1)	11.3 (10.1 - 12.6)
15-20 (High risk)	21.0 (17.7 - 24.7)	16.0 (15.5 - 16.5)	15.4 (13.4 - 17.6)	15.2 (14.7 - 15.8)	16.2 (15.3 - 17.3)	15.8 (13.1 - 18.7)	10.1 (9.0 - 11.5)
> 20 (Very high risk)	4.0 (2.7 - 6.1)	3.8 (3.6 - 4.1)	3.0 (2.2 - 4.2)	2.7 (2.4 - 2.9)	1.1 (0.8 - 1.4)	1.2 (0.6 - 2.4)	1.2 (0.8 - 1.7)
Age (years)							
<45	63.5 (59.2 - 67.5)	59.8 (59.1 - 60.4)	72.2 (69.5 - 74.7)	67.2 (66.5 - 68.0)	86.7 (85.7 - 87.5)	76.6 (73.3 - 79.7)	78.4 (76.7 - 80.0)
≥ 45 to < 55	25.0 (21.5 - 28.9)	22.2 (21.7 - 22.8)	19.4 (17.2 - 21.9)	21.4 (20.7 - 22.0)	9.3 (8.6 - 10.2)	15.4 (12.8 - 18.3)	15.9 (14.5 - 17.5)
≥ 55 to < 65	9.6 (7.4 - 12.5)	13.2 (12.7 - 13.6)	6.3 (5.0 - 7.8)	8.8 (8.3 - 9.2)	3.2 (2.7 - 3.7)	6.5 (4.9 - 8.6)	4.8 (4.0 - 5.7)
≥ 65	1.9 (1.0 - 3.5)	4.8 (4.6 - 5.1)	2.1 (1.4 - 3.2)	2.6 (2.3 - 2.8)	0.8 (0.6 - 1.1)	1.5 (0.8 - 2.8)	0.9 (0.6 - 1.4)
BMI (kg/m^2)							
Normal (<25)	36.2 (32.1 - 40.4)	35.0 (34.3 - 35.6)	32.3 (29.6 - 35.1)	37.5 (36.7 - 38.3)	32.1 (30.8 - 33.4)	38.6 (35.0 - 42.4)	53.8 (51.8 - 55.8)
Overweight (≥ 25 to < 30)	34.8 (30.8 - 39.0)	39.4 (38.8 - 40.1)	30.0 (27.4 - 32.7)	37.1 (36.3 - 37.9)	33.3 (32.0 - 34.6)	32.1 (28.7 - 35.8)	31.1 (29.3 - 33.0)
Obesity (≥ 30)	29.0 (25.3 - 33.1)	25.6 (25.0 - 26.2)	37.7 (34.9 - 40.6)	25.4 (24.7 - 26.1)	34.6 (33.3 - 36.0)	29.3 (25.9 - 32.8)	15.1 (13.7 - 16.6)
Waist circumference (cm)							
Normal (Men, < 94; women, < 80)	45.0 (40.8 - 49.3)	49.5 (48.8 - 50.1)	50.3 (47.3 - 53.2)	49.9 (49.1 - 50.7)	38.0 (36.7 - 39.4)	47.1 (43.3 - 50.9)	59.6 (57.6 - 61.6)
Moderately high WC (Men, ≥ 94 to < 102; women, ≥ 80 to < 88)	34.4 (30.5 - 38.6)	32.5 (31.9 - 33.1)	33.0 (30.3 - 35.8)	33.0 (32.2 - 33.7)	31.4 (30.1 - 32.7)	35.3 (31.8 - 39.0)	30.2 (28.4 - 32.1)
Abdominal obesity (Men, ≥ 102, women ≥ 88)	20.6 (17.3 - 24.3)	18.0 (17.5 - 18.5)	16.7 (14.7 - 19.0)	17.1 (16.5 - 17.7)	30.6 (29.3 - 31.9)	17.6 (14.9 - 20.7)	10.2 (9.0 - 11.5)
≥ 30 min of physical activity/day							
No	64.4 (60.2 - 68.4)	58.8 (58.2 - 59.5)	52.2 (49.3 - 55.1)	52.4 (51.6 - 53.2)	69.3 (68.1 - 70.6)	57.2 (53.4 - 60.9)	48.2 (46.2 - 50.2)
Yes	35.6 (31.6 - 39.8)	41.2 (40.5 - 41.8)	47.8 (44.9 - 50.7)	47.6 (46.8 - 48.4)	30.7 (29.4 - 31.9)	42.8 (39.1 - 46.6)	51.8 (49.8 - 53.8)
Daily vegetables/fruits intake							
No	39.4 (35.3 - 43.7)	33.9 (33.3 - 34.5)	49.6 (46.7 - 52.5)	42.1 (41.3 - 42.9)	62.3 (60.9 - 63.6)	49.9 (46.1 - 53.7)	42.1 (40.1 - 44.1)
Yes	60.6 (56.3 - 64.7)	66.1 (65.5 - 66.7)	50.4 (47.5 - 53.3)	57.9 (57.1 - 58.7)	37.7 (36.4 - 39.1)	50.1 (46.3 - 53.9)	57.9 (55.9 - 59.9)
Use of blood pressure medication							
No	80.8 (77.2 - 83.9)	78.6 (78.1 - 79.2)	78.5 (76.0 - 80.8)	82.1 (81.4 - 82.7)	90.1 (89.2 - 90.9)	80.2 (77.0 - 83.1)	80.4 (78.7 - 82.0)
Yes	19.2 (16.1 - 22.8)	21.4 (20.8 - 21.9)	21.5 (19.2 - 24.0)	17.9 (17.3 - 18.6)	9.9 (9.1 - 10.8)	19.8 (16.9 - 23.0)	19.6 (18.0 - 21.3)
History of high blood glucose							
No	66.9 (62.8 - 70.8)	76.5 (75.9 - 77.1)	76.5 (73.9 - 78.8)	79.6 (79.0 - 80.2)	78.3 (77.2 - 79.4)	73.9 (70.4 - 77.1)	75.5 (73.7 - 77.2)
Yes	33.1 (29.2 - 37.2)	23.5 (22.9 - 24.1)	23.5 (21.2 - 26.1)	20.4 (19.8 - 21.0)	21.7 (20.6 - 22.8)	26.1 (22.9 - 29.6)	24.5 (22.8 - 26.3)

(Continued)

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TABLE 5 Continued

	Chile	Brazil	Central America *	Mexico	Peru	Ecuador	Colombia
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Family history of diabetes							
No	35.2 (31.2 - 39.4)	33.0 (32.3 - 33.6)	26.2 (23.7 - 28.9)	22.8 (22.2 - 23.5)	35.0 (33.7 - 36.3)	31.4 (28.0 - 35.0)	38.4 (36.4 - 40.3)
Second degree relatives[2] (yes)	36.0 (32.0 - 40.2)	37.3 (36.7 - 38.0)	40.7 (37.8 - 43.6)	40.5 (39.7 - 41.2)	39.9 (38.6 - 41.3)	43.9 (40.2 - 47.7)	42.9 (40.9 - 44.9)
First degree relatives[3] (yes)	28.8 (25.1 - 32.9)	29.7 (29.1 - 30.3)	33.1 (30.4 - 35.9)	36.7 (35.9 - 37.5)	25.1 (23.9 - 26.3)	24.7 (21.6 - 28.2)	18.7 (17.2 - 20.4)

Frequencies are expressed as percentages and 95% CI and differences were considered when no 95% CI overlap was detected. [1]Data from Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica, Panama, Dominican Republic, Jamaica, Trinidad and Tobago, Bahamas, Barbados, Aruba, and Curaçao were aggregated as Central America region. [2]Second degree relatives include grandparents, aunt, uncle or first cousin. [3]First degree relatives include parents, brother, sister, or own child.
BMI, Body mass index; CI, Confidence Interval; FINDRISC, Finnish Diabetes Risk Score; WC, waist circumference.

change. Notwithstanding a high intake of fruits and vegetables, Chile was the country with the highest risk of T2D (25%) in this study probably related to the high prevalence of abdominal obesity. It should be noted that in Peru, despite having a relatively high proportion of young subjects, had the highest frequency of abdominal obesity, sedentary lifestyle, no daily intake of fruits and vegetables, and the second highest frequency of obesity. The highest proportion of obesity was found in Central America (37.7%) where the proportion of high T2D risk was 18.4%. In contrast, Colombia was the country with the lowest T2D risk (11.4%) and commensurately lowest obesity, abdominal obesity, and sedentary lifestyle prevalence rates. A systematic review that included five population-based studies in three LA countries (Mexico, Brazil, and Peru) found that the most common predictors of T2D were age, WC, and family history of diabetes (43). Using the β-coefficients of the original FINDRISC model, it is estimated that 54% of the FINDRISC score is attributed to modifiable risk factors (18), and of these, almost 80% is related to increased adiposity amount. The implication here is that prevention imperatives to reduce T2D risk should prioritize weight reduction tactics. In 1079 subjects receiving lifestyle intervention and followed for a mean of 3.2 years in the Diabetes Prevention Program, there was a 16% reduction in T2D incidence for every kilogram of weight lost (57). Lifestyle interventions in patients with prediabetes for 2-6 years have been shown to reduce the incidence of T2D by 27-67% in various ethnicities (58–60). Interventions with T2D medications (e.g., metformin, acarbose, rosiglitazone, pioglitazone, glargine, and semaglutide) for 1.5-6 years have reduced the incidence of T2D between 20-72% (58, 61). Likewise, anti-obesity medications taken for 1.2-4 years reduced the incidence of T2D between 19-79% (62).

In 2017, an expert group recommended using FINDRISC as a screening tool to detect impaired glucose metabolism in Latin America (63); this recommendation was included in some T2D clinical practice guidelines (CPG) in the region. Local validation of the FINDRISC's cutoff was reported in 2019 and proposed for the T2D CPG in Venezuela (16). CPGs from Colombia (64, 65), Brazil (66), Ecuador (67), Uruguay (68), Mexico (69), Argentina (70), and the Diabetes Latin American Association (ALAD) (71) have all adopted the recommendation of using FINDRISC for T2D screening, whereas the CPG in Peru (72) and Chile (73) have not. Criticisms of incorporating FINDRISC as part of organized screening argue that the downstream costs due to further testing and medication may not be justified. The implications of the lower specificity will result in unnecessary tests. Still, we assume that these additional costs are estimated to be much lower than the future treatment costs of the complications of an undiagnosed diabetes patient. Moreover, similar to the narrative about prediabetes and the development of the DBCD model, subsequent actions should be limited to simple diagnostics (FBG, OGTT, and/or A1C) and lifestyle interventions, reserving pharmacotherapy and procedures for guideline-directed management (74).

Internet coverage varies among the different Latin American countries. A limited access to the internet may affect equity in T2D screening in different regions of a country. With an average internet access rate of 68.8 percent in Latin America, the subregion of South America had the highest online access, with around 75 percent of its population having access to the web (75). However, access to the web has been shown to increase during the last decade and we believe that strategies like the one described in this manuscript may be used as a very cost-effective tool to screen people at high risk of diabetes. Finally, using artificial intelligence programs included in META (Instagram, Facebook, and WhatsApp), a direct response ad may be used to reach vulnerable and disadvantaged populations (older, low socioeconomic status, lower educational status). Online diabetes risk tools should be made available at institutions, organizations, and governmental agencies, as well as other primary healthcare settings working in T2D screening and prevention and be part of formal T2D preventive care programs. E-Health risk screening programs might facilitate the follow-up of T2D high-risk patients since their data may be available to the health system.

The strengths of the present study are related to the large-scale organized infrastructure, expedient implementation across diverse populations in Latin America and the Caribbean, and the use of social media platforms. Limitations are related to the self-reported nature of information collected and the associated potential bias. Specifically, people tend to underestimate reported anthropometric

measures and overestimate reported healthy lifestyles. Also, since the FINDRISC is a prognostic tool, no inferences can be made about the true, overall prevalence of T2D or glucose metabolism disorders. A positive FINDRISC requires confirmation by diagnostic testing. In addition, this study consists of a non-probabilistic sample, so the results cannot be generalized to the overall population, thus limiting external validity. Lastly, the asymmetric distribution of the studied population in the region limits comparability and generalizations across the individual countries. In fact, the results could have also been confounded by the younger median ages of certain populations since they would more likely use social networks and eHealth technologies.

This study has important clinical and public health implications. The detection of early stages of DCBD (i.e., insulin resistance and prediabetes) by FINDRISC provides a screenshot of non-modifiable and modifiable risk factors that can be used to assess risks for many different chronic disease states. Online diabetes risk tools should be made available at institutions, organizations, and governmental agencies, as well as other primary healthcare settings working in T2D screening and prevention and be part of formal T2D preventive care programs. As in this study younger people were more likely to use the on-line screening tool, it is important to develop strategies to include older populations as well that are less familiar with the use of social media and the web in general. Thus, future studies should focus on optimizing this process with population-based cohort studies that incorporate transculturalization of lifestyle interventions mitigating DBCD progression across all age groups.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

Conceptualization, MR, RN-M, NB; methodology, MR; plan analysis, RN-M, NB; writing - original draft preparation, RN-M, NB; writing - review and editing, RN-M, NB, AG, AA, JM; final review, RN-M, NB, AG, JM. RN-M and NB share first authorship. All authors contributed to the article and approved the submitted version.

Acknowledgments

The authors are grateful to all subjects of the study.

Conflict of interest

RN-M, NB, and JM received honoraria from Merck for working on this manuscript and have received honoraria for lectures in the past. The authors declare that this study received funding from Merck. Merck funded and designed the study, assisted in collecting the results and paid for the article processing charge.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 28 June 2023
DOI 10.3389/fendo.2023.1166147

OPEN ACCESS

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RECEIVED 14 February 2023
ACCEPTED 05 June 2023
PUBLISHED 28 June 2023

CITATION
Bracco PA, Schmidt MI, Vigo A, Mill JG, Vidigal PG, Barreto SM, Sander MdF, da Fonseca MdJM and Duncan BB (2023) Optimizing strategies to identify high risk of developing type 2 diabetes. *Front. Endocrinol.* 14:1166147. doi: 10.3389/fendo.2023.1166147

Optimizing strategies to identify high risk of developing type 2 diabetes

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Introduction: The success of diabetes prevention based on early treatment depends on high-quality screening. This study compared the diagnostic properties of currently recommended screening strategies against alternative score-based rules to identify those at high risk of developing diabetes.

Methods: The study used data from ELSA-Brasil, a contemporary cohort followed up for a mean (standard deviation) of 7.4 (0.54) years, to develop risk functions with logistic regression to predict incident diabetes based on socioeconomic, lifestyle, clinical, and laboratory variables. We compared the predictive capacity of these functions against traditional pre-diabetes cutoffs of fasting plasma glucose (FPG), 2-h plasma glucose (2hPG), and glycated hemoglobin (HbA1c) alone or combined with recommended screening questionnaires.

Results: Presenting FPG > 100 mg/dl predicted 76.6% of future cases of diabetes in the cohort at the cost of labeling 40.6% of the sample as high risk. If FPG testing was performed only in those with a positive American Diabetes Association (ADA) questionnaire, labeling was reduced to 12.2%, but only 33% of future cases were identified. Scores using continuously expressed clinical and laboratory variables produced a better balance between detecting more cases and labeling fewer false positives. They consistently outperformed strategies based on categorical cutoffs. For example, a score composed of both clinical and laboratory data, calibrated to detect a risk of future diabetes ≥20%, predicted 54% of future diabetes cases, labeled only 15.3% as high risk, and, compared to the FPG ≥ 100 mg/dl strategy, nearly doubled the probability of future diabetes among screen positives.

Discussion: Currently recommended screening strategies are inferior to alternatives based on continuous clinical and laboratory variables.

KEYWORDS

type 2 diabetes, screening strategies, screening tool, mass screening, prediction score, sensitivity, positive predictive value

1 Introduction

The effectiveness of early treatment to prevent diabetes (1, 2) has led medical associations and expert groups to recommend screening (3, 4) and countries to initiate national diabetes prevention programs (5–7). However, defining high risk is challenging. Recommended definitions are traditionally based on one or more established cutoffs of glycemic tests (3, 8, 9). Screening questionnaires have also been applied alone or together with laboratory results (5, 10–12). Clinical prediction scores have also been developed (13–16). However, direct, head-to-head comparisons of the diagnostic metrics of more sophisticated prediction score-based approaches with those of nationally recommended screening strategies are absent.

Our objective was to validate and compare diagnostic metrics of several screening strategies—those currently recommended in three countries with national screening programs (the United States, the United Kingdom, and Finland) and score-based strategies to detect high-risk individuals for primary diabetes prevention.

2 Methods

2.1 Study design, study population, and ethics approval

The ELSA-Brasil cohort study enrolled 15,105 public servants aged 35–74 between 2008 and 2010 (17) and conducted two return evaluations in 2012–2014 and 2016–2018 (18). The Research Ethics Committees approved the study protocol at each investigation site, and all participants gave written consent. Using standardized questionnaires and protocols, we obtained sociodemographic and clinical data (hereafter denominated "clinical variables") (19, 20).

We ascertained diabetes at baseline and follow-up visits by self-report, antidiabetic medication use, and three laboratory measures —fasting plasma glucose (FPG) ≥ 126 mg/dl (7 mmol/L), 2-h plasma glucose (2hPG) ≥ 200 mg/dl (11.1 mmol/L) in a standard oral glucose tolerance test (OGTT), and glycated hemoglobin (HbA1c) ≥6.5% (48 mmol/mol). We considered a prevalent case at baseline when any of these criteria were present. To be consistent with clinical recommendations, we required confirmation of our incident diabetes cases. We thus ascertained incident diabetes only if at least one of these five criteria were present at both follow-up visits or at least two were found at a single visit. Research staff ascertaining diabetes at follow-up were unaware of baseline laboratory values. We considered those who met two criteria at the first follow-up but none at the second follow-up as not having developed diabetes. We excluded those without data for incident diabetes due to death, who lack follow-up, or with incomplete data from analyses.

2.2 Recommended screening strategies evaluated

We first assessed screening strategies based on traditional laboratory cutoffs for pre-diabetes (intermediate hyperglycemia) (3, 8, 21). Next, we evaluated additional screening recommendations used in national diabetes prevention programs. In addition to the United States, the United Kingdom and Finland have ongoing national programs (5, 12, 22). The American Diabetes Association (ADA) recommends two screening options (3). Considering that our sample begins at age 35, the first is a one-step (test all) approach directly measuring glycemia or HbA1c. The second applies a two-step approach in which those positive on a questionnaire are considered at high risk if they present FPG ≥ 100 mg/dl or HbA1c ≥ 5.7% (39 mmol/mol) in subsequent testing (3). The Centers for Disease Control and Prevention (CDC) recommends screening with either the ADA approach or just the ADA questionnaire (22). For the United Kingdom, the National Institute for Health and Care Excellence (NICE) recommends a two-step strategy—a clinical score followed by lab testing for those above its cutoff (FPG ≥ 99 mg/dl or an HbA1c ≥ 6.0% [42 mmol/mol]) (12). The Finnish strategy considers all those with a FINDRISC questionnaire score ≥15 as high risk (5, 23). Applying ELSA cohort follow-up data, we compared the diagnostic properties of these strategies with those of the scored-based screening strategies that we developed.

2.3 Statistical analysis

We randomly divided our sample equally into training and validation datasets. We described our sample characteristics calculating either the mean (standard deviation) or mean (95% confidence interval) for continuous variables and the absolute frequency (percentage; 95% confidence interval) for discrete variables. We used logistic regression on the training dataset to develop risk functions to predict incident diabetes. We initially produced models only with clinical variables, keeping those that

significantly improved the area under the receiver operating characteristic (AUC) curve. We considered age, sex, self-reported ethnicity, educational attainment, parental history of diabetes, daily consumption of fruits or vegetables, leisure-time physical activity (at least 150 min per week of moderate- or vigorous-intensity physical activity), smoking, hypertension or self-reported use of hypertension medication, body mass index (BMI), and waist circumference. We then selected the best of these derived risk functions to calculate the probability of developing diabetes for each participant in our validation dataset. Using this same approach, we next evaluated risk scores composed of laboratory results and their combination with the clinical data. We provide risk function formulas in the Supplementary Material. Additionally, we built an online tool using R Shiny (http://elsabrasil.org/funcoes-de-risco/risco-diabetes-10-anos/) for risk calculation based on scores composed of different combinations of variables to predict the 10-year risk of developing diabetes to be made available to the public.

These risk scores, different from categorical rule approaches, for which cutoff points have already been defined (e.g., the ADA questionnaire ≥5; FPG ≥ 100 mg/dl) (3, 12, 22), have no *a priori* cutoff. To evaluate their properties, we thus defined potential cutoffs based on their positive predictive value (PPV), selecting ones where being positive reflected 20% and alternatively 15% probabilities of developing diabetes over our sample's follow-up. These were close to the probabilities of developing the disease among those labeled by current ADA laboratory testing strategies.

Using the same ELSA database, we also constructed the clinical scores recommended by national strategies. As we lacked information for one of the FINDRISC questions—a previous finding of pre-diabetes—we randomly attributed the presence of prior pre-diabetes to 90% of those with baseline hyperglycemia by WHO criteria.

Finally, in our validation sample, we calculated diagnostic properties for the rules assessed: the percentage deemed at high risk, sensitivity, specificity, and positive and negative (1 – PPV) predictive values. We also report the AUC and the net reclassification index (16). We estimated 95% confidence intervals through normal approximation methods.

3 Results

Our study used data from the 15,105 participants of the ELSA-Brasil cohort. We excluded those with diabetes at baseline (n = 2,429), missing information to ascertain diabetes (n = 5), or missing values for variables we considered in the construction of risk scores (n = 20). We additionally excluded those not returning to follow-up visits (n = 1,971), missing data to ascertain incident diabetes (n = 351), or using oral antidiabetic medication but not reporting to have diabetes (n = 212). Finally, due to our requirement of confirmation of incident cases, we excluded those with no finding of diabetes at the first follow-up and only one criterion present at the second follow-up visit (n = 592). Our final sample thus consisted of 9,525 participants (Figure 1), randomly divided into training and validation samples.

Over a mean (standard deviation) of 7.4 (0.54) years of follow-up, 864 participants developed diabetes. We considered 24 participants who met two criteria for diabetes at the first follow-up but none at the second follow-up as not having developed diabetes. Supplementary Table 1 shows that training and validation datasets had similar distributions of variables considered in building risk scores and a similar (9.1%) incidence of diabetes.

Table 1 compares three cardinal metrics for screening evaluation—the percentage of screen positives (those labeled as high risk), sensitivity (percentage of future incident cases among screen positives), and PPV (percentage of screen positives who developed future diabetes). The complement of PPV (1 – PPV) also evaluates the false-positive rate. The top part of the table shows results for laboratory-based approaches. Since ELSA-Brasil participants were at least age 35 at entry, the one-step ADA laboratory option was to test all and consider positive those above the established laboratory cutoffs for pre-diabetes. If only FPG is tested, though a large percentage (76.6%) of those who developed diabetes were detected, a high percentage (40.6%) were labeled as high risk, most of them (1 – PPV; 82.9%%) not developing diabetes during our follow-up. Similar strategies testing FPG plus HbA1c or 2hPG produced similar results. The previous 2021 ADA recommendation of testing all ≥45 years of age and those younger when presenting specific conditions (evaluated here with only FPG testing) also performed similarly. It identified slightly fewer future

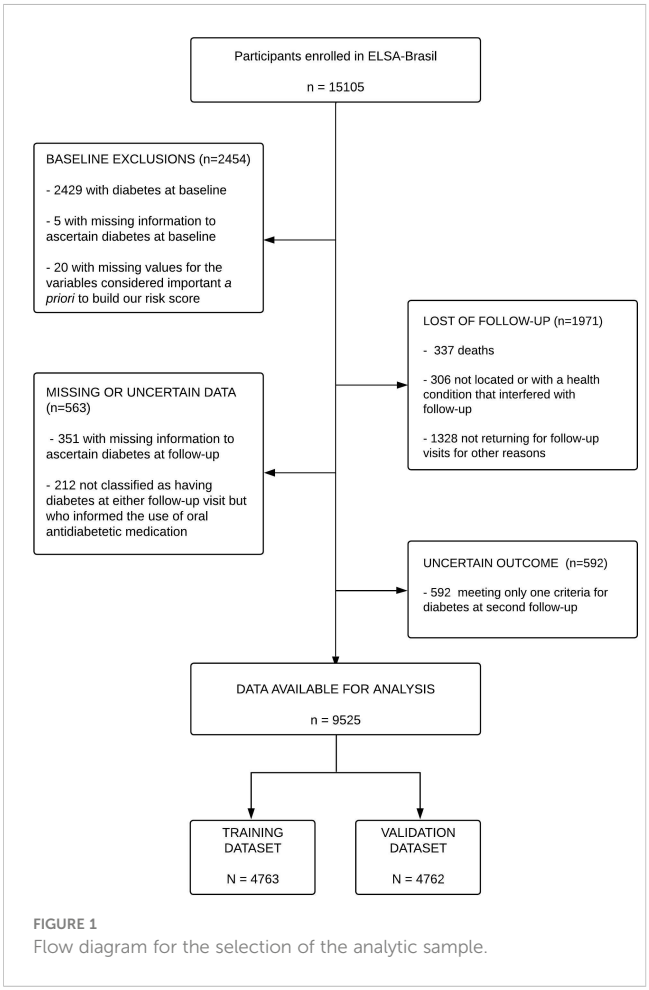

FIGURE 1
Flow diagram for the selection of the analytic sample.

10.3389/fendo.2023.1166147

TABLE 1 Diagnostic properties of currently recommended one- or two-step categorical screening strategies in the ELSA-Brasil validation sample (N = 4762).

	High risk	Sens	PPV
Laboratory only (one-step)	% (95%CI)	% (95%CI)	% (95%CI)
Current ADA: FPG ≥ 100 mg/dl	40.6 (39.2; 42.0)	76.6 (72.6; 80.6)	17.1 (15.4; 18.7)
Current ADA: FPG ≥ 100 mg/dl or 2hPG ≥ 140 mg/dl	47.5 (46.1; 49.0)	86.7 (83.5; 89.9)	16.5 (15.0; 18.1)
Current ADA: FPG ≥ 100 mg/dl or HbA1c ≥ 5.7%	47.2 (45.8; 48.6)	82.3 (78.7; 85.9)	15.7 (14.2; 17.2)
Previous ADA (2021, all aged ≥45)*: FPG ≥ 100 mg/dl	39.8 (38.4; 41.2)	76.1 (72.1; 80.1)	17.3 (15.6; 19.0)
Current WHO: only FPG ≥ 110 mg/dl	11.0 (10.1; 11.9)	40.1 (35.5; 44.8)	33.0 (29.0; 37.0)
Current WHO: FPG ≥ 110 mg/dl or 2hPG ≥ 140 mg/dl	24.9 (23.6; 26.1)	70.2 (65.8; 74.5)	25.6 (23.1; 28.1)
National program strategies			
ADA questionnaire	18.5 (17.3; 19.6)	36.4 (31.8; 40.9)	19.1 (16.4; 21.7)
ADA two-step strategy	13.1 (12.1; 14.1)	34.0 (29.5; 38.5)	24.9 (21.4; 28.4)
NICE two-step strategy	26.8 (25.5; 28.1)	60.4 (55.7; 65.0)	21.3 (19.0; 23.6)
FINDRISC questionnaire	17.8 (16.7; 18.9)	41.5 (36.8; 46.2)	21.2 (18.4; 24.0)

Sens, sensitivity; PPV, positive predictive value; FPG, fasting plasma glucose; ADA, American Diabetes Association; WHO, World Health Organization; HbA1c, glycated hemoglobin; 2hPG, 2-h plasma glucose.
Lipids = triglycerides and high-density lipoprotein cholesterol. ADA questionnaire: risk score ≥5; ADA two-step strategy: risk score ≥5, then FPG ≥ 100 mg/dl or HbA1c ≥ 5.7%; NICE two-step strategy: U.K. Diabetes Risk Score ≥14, then FPG ≥ 99 mg/dl or HbA1c ≥ 6%; FINDRISC questionnaire: risk score ≥15.
*Those under age 45 presenting known risk factors were also tested.

cases (76.1% *vs.* 76.6%) while labeling marginally fewer (39.8% *vs.* 40.6%) as high risk with a slightly lower false-positive rate (82.7% *vs.* 82.9%). Testing all with the WHO fasting glucose cutoff of ≥110 mg/dl labeled considerably fewer participants (11.0%) as high risk and produced fewer false positives (1 – PPF; 67.0%) but identified a lower percentage of future cases (40.1%).

In the lower portion of Table 1, we present and contrast diagnostic properties of additional strategies recommended by national screening programs. The ADA questionnaire alone (AUC = 0.599; 95%CI 0.576–0.623), one of the CDC's recommended screening tests, labeled 18.5% as high risk, but with 80.9% (1 – PPV) of these being false positives while detecting only 36.4% of future cases of diabetes. Assuming a second step testing both FPG and HbA1c, the ADA two-step strategy presented a low AUC (0.615; 95%CI 0.592–0.638), labeled 13.1% as high risk with 75.1% false positives while detecting only 34.0% of those who went on to develop diabetes. Similarly, values for the NICE two-step approach, when combined with the Diabetes U.K. risk questionnaire (AUC = 0.685; 95%CI 0.661–0.710), labeled 26.8%, with 78.7% false positives and 60.4% of future cases detected. The FINDRISC questionnaire (AUC = 0.630; 95%CI 0.606–0.655) labeled 17.8%, with 78.8% false positives and 41.5% of future cases being detected. Supplementary Table 2 presents an expanded array of diagnostic properties for these and other one-step laboratory testing strategies.

Next, we evaluated the clinical scores that we had developed. The best score is based only on readily available clinical variables of modeled risk as a function of age, sex, self-declared ethnicity, BMI, waist circumference, hypertension, and parental history of diabetes (AUC = 0.754; 95%CI 0.732–0.777). Further adjustment with other diabetes risk factors did not improve this score.

We additionally evaluated similarly derived prediction rules composed of laboratory tests, alone or combined with clinical variables, expressing these laboratory variables continuously rather than categorically based on recommended cutoffs. For these analyses, we initially defined high risk as a 20% probability of developing diabetes over our 7.4-year average follow-up. Figure 2 illustrates the marked increase in the percentage of the ELSA-Brasil validation sample developing incident diabetes across risk deciles produced by four continuous variable strategies. Of note, all four prediction rules—clinical variables only, FPG only, clinical variables plus FPG, and clinical variables adding HbA1c and lipids along with FPG—distinguished those at minimal risk (risk close to 0%, first two deciles) from those at very high risk (35% to >40%, top decile). Scores combining clinical and laboratory tests placed more than 60% of those who developed diabetes in the top two deciles of estimated risk.

Table 2 presents the same diagnostic properties above for several continuous variable rules, including those based on two-step approaches (clinical variable score first, then laboratory testing for those above an initial risk cutoff). With a score cutoff identifying a 20% probability of developing future diabetes, these rules labeled a considerably lower percentage of the sample—between 10.9% and 15.3%—as high risk than most nationally recommended strategies. That based only on clinical variables performed poorly, identifying only 31.6% of future cases. Adding FPG testing to clinical variables considerably improved future case detection to 49.7%, and further adding HbA1c, triglycerides, and HDL-c tests raised it to 54.5%. The two-step approach—laboratory testing only in those at highest risk based on clinical variables—reduced laboratory testing but with some loss in future case detection. For example, testing with FPG only the 50% or 67% at highest clinical risk (*vs.* testing all) identified

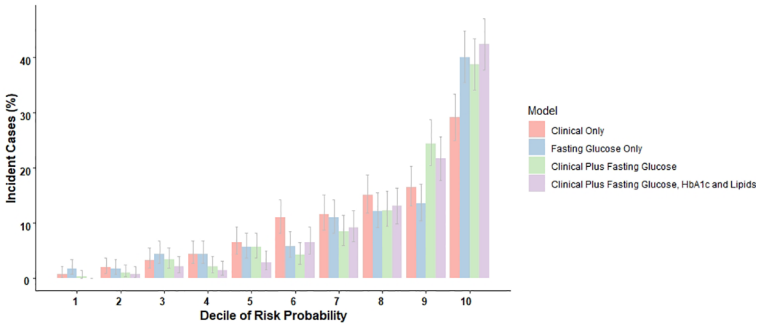

FIGURE 2
The distribution of incident cases during an average of 7.4 years of follow-up across deciles of risk, as predicted by rules with just clinical variables, just fasting glucose, and combinations of both with and without additional laboratory determinations. ELSA-Brasil validation sample, N = 4,762.

43.8% and 48.0% (*vs.* 49.7%) of future cases, respectively, while labeling as positive slightly smaller percentages (13.1% and 14.1% *vs.* 14.7%). Adding HbA1c and lipids improved future case detection slightly (48.7% and 53.1%).

When we lowered the score positivity cutoff to a 15% probability of future diabetes, rules identified considerably more future cases at the cost of labeling more of the sample as high risk. The clinical score alone performed better at this lower cutoff, labeling 20.1% at high risk

TABLE 2 Diagnostic properties of continuous variable, one-step, and two-step screening strategies based on a clinical score and selected laboratory tests, as developed and validated in ELSA-Brasil.

Continuous variable strategies	Only clinical strategy			+FPG			+FPG, HbA1c, lipids		
	High risk	Sens	PPV	High risk	Sens	PPV	High risk	Sens	PPV
≥20% probability of developing diabetes	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)
Test all	10.9 (10.0; 11.8)	31.6 (27.2; 35.9)	26.2 (22.4; 29.9)	14.7 (13.7; 15.7)	49.7 (44.9; 54.4)	30.6 (27.2; 34.0)	15.3 (14.3; 16.3)	54.5 (49.8; 59.2)	32.3 (28.9; 35.7)
First clinical score[a], then combined with lab test(s) for									
67% of the sample at highest clinical risk				14.1 (13.1; 15.1)	48.0 (43.3; 52.7)	30.8 (27.3; 34.2)	14.7 (13.7; 15.7)	53.1 (48.4; 57.8)	32.8 (29.3; 36.2)
50% of the sample at highest clinical risk				13.1 (12.1; 14.0)	43.4 (38.7; 48.1)	30.1 (26.5; 33.7)	13.5 (12.5; 14.5)	48.7 (44.0; 53.4)	32.7 (29.0; 36.3)
33% of the sample at highest clinical risk				11.0 (10.1; 11.9)	35.0 (30.5; 39.6)	28.9 (25.0; 32.8)	11.3 (10.4; 12.2)	38.3 (33.7; 42.9)	30.7 (26.8; 34.6)
≥15% probability of developing diabetes									
Test all	20.1 (18.9; 21.2)	45.9 (41.2; 50.6)	20.7 (18.1; 23.3)	20.3 (19.2; 21.5)	64.0 (59.5; 68.6)	28.5 (25.6; 31.3)	20.7 (19.6; 21.9)	65.0 (60.5; 69.5)	28.4 (25.6; 31.2)
First clinical score[a], then combined with lab test(s) for									
67% of the sample at highest clinical risk				19.5 (18.4; 20.6)	61.7 (57.1; 66.3)	28.6 (25.7; 31.5)	19.7 (18.6; 20.9)	63.1 (58.6; 67.7)	29.0 (26.1; 31.9)
50% of the sample at highest clinical risk				17.6 (16.6; 18.7)	56.6 (51.9; 61.3)	29.1 (26.0; 32.1)	17.9 (16.8; 19.0)	58.0 (53.4; 62.7)	29.3 (26.3; 32.4)
33% of the sample at highest clinical risk				14.6 (13.6; 15.6)	45.2 (40.5; 49.9)	28.1 (24.8; 31.5)	14.5 (13.6; 15.6)	46.2 (41.5; 50.9)	28.7 (25.3; 32.1)

Training sample N = 4,763. Validation sample, N = 4,762.
FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; PPV, positive predictive value.
[a]A probability of developing diabetes over 7.4 years using just the clinical score of ≥6.5% initially selects 67% of the sample, one of ≥8.9% selects 50% of the sample, and one of ≥12% selects 33% of the sample.

and identifying 45.9% of those developing future diabetes. Adding FPG to this screening approach labeled 20.3% at high risk and identified 64.0% of future cases, and adding HbA1c and lipids labeled 15.3% at high risk and identified 65.0% of future cases. Testing FPG in only the 50% or 67% at highest clinical risk using the 15% cutoff identified slightly lower percentages (56.6% and 61.7% *vs.* 64.0%) of future cases, with marginally fewer labeled as positive (17.6% and 19.5% *vs.* 20.3%). Additionally adding HbA1c and lipids in these two-step approaches improved future case identification to 58.1% and 63.1%, respectively.

Two-step approaches, which advanced to laboratory testing only in the 33% at highest clinical risk while producing lower percentages (11.0% to 14.6%) of participants being labeled high risk, detected considerably fewer future cases (35.0% to 45.2%).

Compared with recommended one- or two-step categorical approaches presented in Table 1, continuous variable risk score strategies incorporating both clinical variables and glycemic testing labeled fewer individuals at high risk. As such, they created fewer false positives while still identifying a significant fraction of future cases. For example, when testing only the 67% at the highest clinical risk with FPG, HbA1c, and lipids, a 20% probability cutoff rule labeled only 14.7% as positive (*vs.* 47.2% for the ADA FPG and HbA1c lab-only strategy) and doubled the probability of developing diabetes among those at high risk (PPV = 32.8% *vs.* 15.7%) while detecting 53.1% of future cases. This strategy also compared favorably with the ADA two-step categorical approach, identifying more future cases (53.1% *vs.* 34.0%) while labeling only a slightly higher percentage as high risk (14.7% *vs.* 13.1%). Those labeled were more likely to develop diabetes (32.8% *vs.* 24.9%). Adding the 2hPG of an OGTT instead of an HbA1c as the additional laboratory test produced little benefit in strategies that included clinical variables and lipids (data not shown).

Of note, all of these continuous variable strategies presented PPVs, though higher than almost all of the categorical approaches, well below 50%, indicating the presence of many false positives. High false positivity was especially notable using a 15% cutoff or only the clinical score. False-positive rates (1 − PPVs) were usually ~5%–10% lower with the 20% probability cutoff.

Supplementary Table 3 (for the 20% probability of developing diabetes cutoff) and Supplementary Table 4 (for the 15% probability cutoff) present an expanded array of diagnostic properties for various one-step continuous variable strategies using laboratory testing, the clinical score, or both. As can be seen, the AUCs for continuous variable strategies were superior to those based only on categorical glycemic cutoffs, with the more elaborate continuous approaches achieving AUCs of ~0.85.

4 Discussion

We compared different screening strategies for diabetes in adults ≥ 35 years using easily obtainable clinical variables and laboratory results. Our findings showed that risk scores combining clinical variables and glycemic measures expressed continuously outperformed traditional laboratory-based categorical approaches and the two-step categorical approaches frequently recommended in national screening programs. Combining a continuously expressed FPG with clinical variables resulted in the largest gain in accuracy. Including additional laboratory results produced some further improvement. While all strategies identified considerably more false than true positives, those based on continuously expressed variables had a more balanced mix between greater future case detection and less false-positive labeling. Finally, using two-step strategies, with the first step evaluating only clinical variables to identify those initially at the highest risk and the second step adding laboratory testing only for those identified, considerably reduced the need for laboratory testing.

Three major national programs of diabetes prevention have defined specific rules to label high risk and initiate preventive intervention. In the United States, the CDC recommends lifestyle counseling for overweight individuals at high risk based on the ADA questionnaire, an ADA lab cutoff, or having a previous pregnancy complicated by gestational diabetes (22). The United Kingdom's National Health Service recommends intervention for those positive with the two-step NICE screening strategy (12). The Finnish Diabetes Prevention Program (DPP) recommends using a score of ≥15 points on the FINDRISC questionnaire to identify high risk while also considering at high risk those with OGTT results above WHO cutoffs or a history of either coronary heart disease or previous gestational diabetes (5).

Our findings indicate that the UK/NICE and especially the CDC/ADA approaches label a relatively high percentage of the sample as high risk, producing many referrals, a significant fraction of whom will not develop diabetes in the subsequent decade. Additionally, as shown in Figure 3, the approaches using ADA laboratory cutoffs, the ADA questionnaire, or both are internally inconsistent. Directly applied ADA glycemic testing labeled nearly 50% as high risk, but the ADA questionnaire labeled only 18% and the two-step approach only 13%. While the directly applied laboratory testing identified ~80% of cases, the questionnaire and two-step approaches identified little more than one-third of cases. The Finnish approach to screening, which sums those meeting other entry criteria with those presenting a high FINDRISC score, will likely also label a relatively high percentage as high risk and produce many false positives. Additionally, the two-step categorical strategies involving questionnaires and laboratory testing, as recommended by U.S. and U.K. authorities, were inferior to a similar continuous variable risk score as shown in the right panels of the figure. The continuous variable score labeled a smaller fraction of the population as at high risk than all but the ADA two-step strategy and produced a greater probability of those so labeled going on to develop diabetes than any of the other approaches.

As has been noted (24), almost all cost-effectiveness studies of screening followed by lifestyle interventions to prevent diabetes have been based on intensive interventions in non-community clinical trial settings. The effectiveness shown in these studies diminishes with their translation to community settings with less intensive interventions. With the use of the nationally recommended screening approaches, community programs also frequently recruit participants at lower risk of incident diabetes than those of the original clinical trials (2). This combination of a

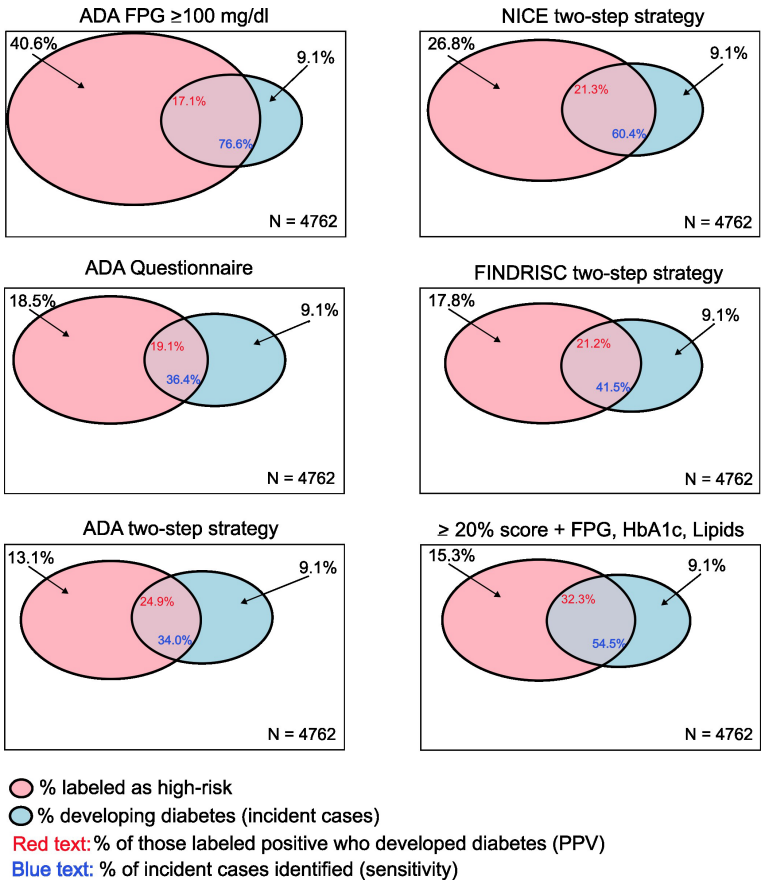

FIGURE 3
Graphical representation of three principal diagnostic metrics of different screening strategies. The box of each panel represents the whole sample. The red (left) circles represent the percentage of the sample who screened positive (labeled high risk) using each screening strategy, and the blue (right) circles represent the percentage of the sample who developed diabetes over follow-up. Positive predictive value (probability of those labeled as positive progressing to incident diabetes) is depicted by the percentage of the red circle intersecting with the blue circle (red number in the intersection), and screening test sensitivity (percentage of future incident cases identified) is depicted by the percentage of the blue circle within the red circle (blue number in the intersection).

lower effectiveness of the intervention and a lower *a priori* probability of participants developing diabetes can markedly reduce the gains of screening. Lifestyle intervention in community settings, primarily in North America, has been estimated to prevent diabetes in only 3% of those enrolled (2). Improved titration of high-risk labeling through full use of clinical and laboratory information would improve the absolute probability of preventing diabetes through early detection. Hopefully, identifying additional influential risk factors from dietary, proteomic, DNA methylation, or metabolomic sources will permit further improvement of prediction. However, this gain may come at the cost of more sophisticated and thus more time-consuming and expensive strategies. Further, future advances in understanding the role of diet (25) and other factors in the pathogenesis of diabetes and in leading those with unhealthy habits to modify their human behavior will permit refinement in dietary and other lifestyle interventions.

The use of continuous variable screening strategies, here documented to be superior, as additionally found by another recent study (26), combined with patient preferences, seems more consistent with the current vision of precision and personalized medicine. To that end, Table 3 presents practical, clinically relevant implications derived from our study. Frequent rescreening should mitigate the concern that the continuous variable rules shown here will detect fewer future cases than current ADA one-step approaches. The ADA recommends testing adults over 35 or presenting risk factors every 3 years and those with previously detected pre-diabetes every year (3).

A potential limitation to our study is that our rules using HbA1c performed relatively poorly, suggesting that greater laboratory error in HbA1c determination, although not reflected in our evaluation of its reliability coefficient (27), could have been present. Such imprecision could have led to underestimating the benefit of including HbA1c in strategies. Additionally, as in all evaluations of clinical predictive rules, our results are based on our sample's pretest probability—the probability of developing diabetes over a 7.5-year follow-up. Settings with considerably greater or lesser incidence would need to calibrate our rules to their population's risk of developing diabetes. However, as shown by the Global Burden of Disease Study, the incidence of type 2 diabetes is not greatly different in Brazil than in most other parts of the world (Supplementary Figure 1).

TABLE 3 Main clinically relevant implications from findings based on diagnostic properties of screening strategies in the ELSA-Brasil validation sample.

• Combining sociodemographic and clinical factors with laboratory tests produces the best screening rules.
• Algorithms based on continuously expressed variables, made available *via* digital calculators, produce a better balance between detecting more future cases and creating fewer false positives.
• Fasting glucose is best among available laboratory tests considering feasibility, accuracy, and cost issues.
• When feasible, including glycated hemoglobin, HDL-c, and triglycerides will provide additional prediction in screening.
• Two-step strategies, first identifying those at higher risk based only on readily available clinical information and then testing them for hyperglycemia, can reduce laboratory testing with minimal loss in detecting future cases.

HDL-c, high-density lipoprotein cholesterol.

Our study presents several strengths. Its outcome of future incident diabetes and its focus on the most relevant screening metrics permit clinically relevant, head-to-head comparisons of different strategies. Our ascertainment of diabetes required confirmation, approximating it to the clinical definition, giving our findings greater generalizability. Standardized collection of data and centralized laboratory measurement add quality and precision to our results. Our relatively large sample size allows for more precise estimates of diagnostic properties. Rates of obesity and central obesity and other diabetes risk factors in ELSA-Brasil, being a contemporary cohort, are more in line with their current prevalence, permitting more easily generalizable clinical scores. Finally, our provision of an online calculator permits immediate use of findings.

5 Conclusions

All evaluated screening strategies to predict future diabetes are far from perfect. However, risk scores combining clinical variables with glycemic measures expressed in a continuous form are superior to traditional screening strategies and currently recommended two-step categorical strategies. National programs and those making recommendations should favor continuous variable scores in their recommended screening strategies to maximize the potential benefit for those invited to screening programs while guaranteeing an adequate balance between benefits and costs. They should also make explicit the impact of their screening strategy recommendations in terms of the percentage labeled as high risk and the probability that those so labeled, without intervention, will develop diabetes in the foreseeable future.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Comitê de Ética em Pesquisa do Hospital de Clínicas de Porto Alegre. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Concept and design: PB, MS, and BD. Acquisition, analysis, or interpretation of data: PB, MS, AV, JM, PV, SB, and BD. Drafting of the manuscript: PB and BD. All authors made critical revisions to the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

Funding

The study was supported by the Brazilian Ministry of Health (Department of Science and Technology); the Ministry of Science, Technology, and Innovation (FINEP, Financiadora de Estudos e Projetos), grant nos. 01 06 0010.00, 01 06 0212.00, 01 06 0300.00, 01 06 0278.00, 01 06 0115.00, and 01 06 0071.00; and the National Council for Scientific and Technological Development (CNPq). PB received a fellowship from CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior). The funders had no role in the study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the article for publication.

Acknowledgments

The authors thank the staff and participants of ELSA-Brasil for their essential contributions.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1166147/full#supplementary-material

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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 13 July 2023
DOI 10.3389/fpubh.2023.1159024

OPEN ACCESS

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RECEIVED 05 February 2023
ACCEPTED 26 June 2023
PUBLISHED 13 July 2023

CITATION
Crummett LT and Aslam MH (2023) Diabetes websites lack information on dietary causes, risk factors, and preventions for type 2 diabetes.
Front. Public Health 11:1159024.
doi: 10.3389/fpubh.2023.1159024

Diabetes websites lack information on dietary causes, risk factors, and preventions for type 2 diabetes

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Introduction: Type 2 diabetes (T2D) is a growing public health burden throughout the world. Many people looking for information on how to prevent T2D will search on diabetes websites. Multiple dietary factors have a significant association with T2D risk, such as high intake of added sugars, refined carbohydrates, saturated fat, and red meat or processed meat; and decreased intake of dietary fiber, and fruits/vegetables. Despite this dietary information being available in the scientific literature, it is unclear whether this information is available in gray literature (websites).

Objective: In this study, we evaluate the use of specific terms from diabetes websites that are significantly associated with causes/risk factors and preventions for T2D from three term categories: (A) dietary factors, (B) nondietary nongenetic (lifestyle-associated) factors, and (C) genetic (non-modifiable) factors. We also evaluate the effect of website type (business, government, nonprofit) on term usage among websites.

Methods: We used web scraping and coding tools to quantify the use of specific terms from 73 diabetes websites. To determine the effect of term category and website type on the usage of specific terms among 73 websites, a repeated measures general linear model was performed.

Results: We found that dietary risk factors that are significantly associated with T2D (e.g., sugar, processed carbohydrates, dietary fat, fruits/vegetables, fiber, processed meat/red meat) were mentioned in significantly fewer websites than either nondietary nongenetic factors (e.g., obesity, physical activity, dyslipidemia, blood pressure) or genetic factors (age, family history, ethnicity). Among websites that provided "eat healthy" guidance, one third provided zero dietary factors associated with type 2 diabetes, and only 30% provided more than two specific dietary factors associates with type 2 diabetes. We also observed that mean percent usage of all terms associated with T2D causes/risk factors and preventions was significantly lower among government websites compared to business websites and nonprofit websites.

Conclusion: Diabetes websites need to increase their usage of dietary factors when discussing causes/risk factors and preventions for T2D; as dietary factors are modifiable and strongly associated with all nondietary nongenetic risk factors, in addition to T2D risk.

KEYWORDS

diabetes, risk factors, causes, prevention, websites, diet, nutrition

Introduction

Type 2 diabetes (T2D) is a chronic disease characterized by excessive levels of glucose in the blood resulting from the cells' inability to respond to insulin, termed insulin resistance, and an inability of pancreatic beta cells to produce adequate levels of insulin. The International Diabetes Federation (IDF) has stated that the increasing global prevalence of T2D presents a large social, financial, and health system burden across the world (1). The global prevalence of T2D in 20–79 year old adults was estimated at 10.5% in 2022 and it is projected to increase to 12.2% by 2045 (2). A staggering 38% of the adult population in the United States (US) has prediabetes (insulin resistance) and 11.3% have T2D (3). "Adult-onset diabetes" was a commonly used term for T2D because it only affected adults; but that is no longer true. In 2021, there were approximately 41,600 new cases of T2D diagnosed in children, worldwide (4). Considering that only the proximate cause of death appears on death certificates, diabetes-associated deaths may be significantly underestimated (5).

Understanding what factors promote the development of insulin resistance and T2D is imperative in curbing the soaring T2D pandemic. Genetic risk factors for T2D include family history (6), advanced age (2), and non-white ethnicity (7). However, ethnic groups that show a relatively high prevalence of T2D in the US, show a much lower T2D prevalence in their country of origin (7); showing that environmental factors play a critical role in T2D risk. Further, in order to explain the rapid increase in T2D prevalence over the last three decades (8, 9), and reduce the predicted growth of T2D prevalence in the future (2, 8), we need to look beyond genetic (non-modifiable) risk factors for T2D, and focus on dietary and lifestyle-associated risk factors that are modifiable.

A review of 86 meta-analyzes that analyzed risk factors for T2D reported "convincing evidence" for the association between T2D risk and the following modifiable risk factors: low whole grain consumption, metabolically healthy obesity, increased sedentary time, low adherence to a healthy dietary pattern, high level of serum uric acid, which has been associated with high fructose/sugar intake (10–12), low level of serum vitamin D, and decreased conscientiousness (13). A meta-analysis of cohort studies that specifically examined lifestyle-related risk factors for T2D reported the following high-risk factors: obesity, (especially central obesity), metabolic syndrome components (hypertension, dyslipidemia), lack of physical activity, high consumption of sugar-sweetened beverages, processed red meat, refined grains, and alcohol; and low consumption of fruits, vegetables, fiber, and whole grains (14). It is important to note that these dietary risk factors were still significantly associated with T2D after controlling for body mass index (BMI) (14).

Given that dietary factors may be the most amenable to modification to prevent the development of T2D, some recent meta-analyzes of T2D risk factors have focused solely on dietary factors. One study reported significant associations with T2D risk and higher intake of cereal fiber, unsaturated fatty acids, magnesium, and polyphenols; and reduced glycemic load, intake of added sugars, and intake of high-sugar beverages (15). Another study reported a significant negative association with T2D risk and intake of foods associated with a Mediterranean diet, including: whole grains, low-fat dairy products, yogurt, olive oil, chocolate, fiber, magnesium, and flavonoids (16). The same study reported a significant positive association with T2D risk and high glycemic index/load diets, high consumption of red and processed meat, sugar, and artificial sugar-sweetened beverages (16).

To understand how to prevent the development of T2D, many people are likely to search diabetes websites, *via* a Google search, rather than searching scientific journal articles. Based on searching a limited number of diabetes websites, we found limited information on nongenetic (lifestyle-associated) causes/risk factors or preventions for T2D, aside from obesity and lack of physical activity. The observed lack of information on diabetes websites, regarding nongenetic T2D causes/risk factors and preventions, may be anecdotal, or it may point to a real lack of information in the gray literature. To answer this important public health question, we used web scraping and computer code to extract and quantify terms associated with T2D causes/risk factors and preventions from 73 diabetes websites. We quantified the use of terms for T2D causes/risk factors and preventions that were categorized as (A) dietary factors (B) nondietary nongenetic (lifestyle-associated) factors, and (C) genetic (non-modifiable) factors. We determined if term category (dietary, nondietary nongenetic, genetic) or website type (business, government, nonprofit) had a significant effect on the percentage of sites providing specific terms.

Materials and methods

Website selection

In November 2022, we performed a "Google Advanced Search" to search for diabetes websites to analyze. We used the following advanced search criteria, which resulted in 436,000 websites in the search engine results (Figure 1): *All these words: "type 2 diabetes"; this exact word or phrase: "causes" OR "risk" OR "prevention"; none of these words: "pubmed, "doi:," "download pdf," "youtube," "amazon," "advertisement"; Language: English; Region: anywhere; Last update: past year; site or domain: NA; terms appearing: In the text of the page; file type: any format; usage rights: not filtered by license.* The "none of these words" criteria effectively excluded websites associated with academic journals, books, videos, and advertisements. The first 80 websites in the search engine results were selected for analysis (Figure 1). Other studies in which website data from a keyword search were analyzed, selected the first 50–60 websites that appeared in the search engine results (17–20). Eighty websites were reduced to 73 websites after excluding some sites due to one of the following reasons: (1) website was funded by the same organization/company as that of another included website, or (2) one had to click on several links to access relevant information (the information was external to the website), or (3) the site was outside the US and was only accessible within the source country (Figure 1).

Categorization of websites

The 73 websites that were included in the analysis were categorized as business, government, or nonprofit (Supplementary Table S1; Figure 1). Websites owned by for-profit companies were assigned to the business category ($n = 33$) and most had .com domains (Supplementary Table S1). Websites owned by county, state, or federal government were assigned to the government category ($n = 18$) and most had .gov domains (Supplementary Table S1). Websites owned by

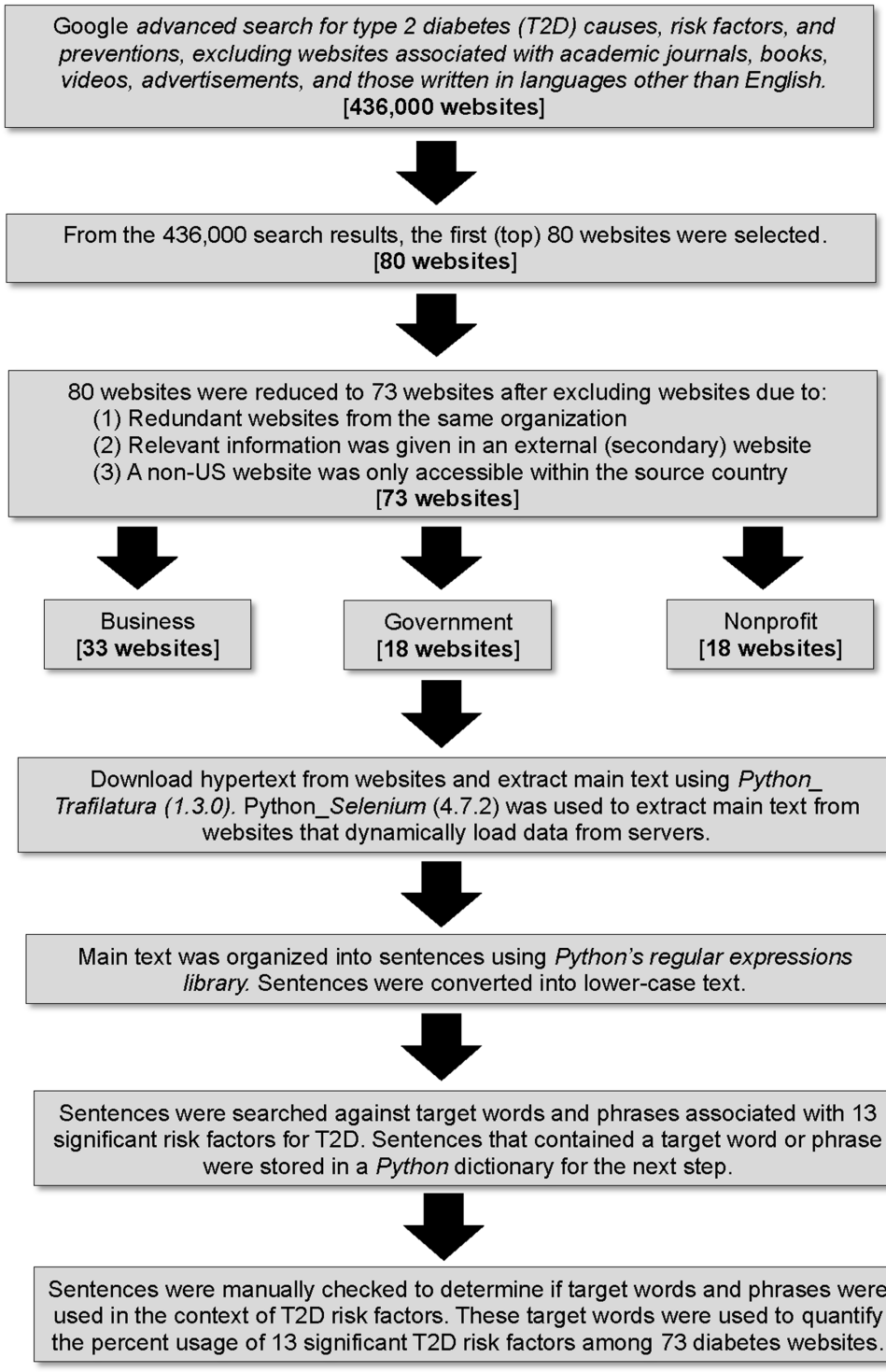

FIGURE 1
Flow diagram illustrating methodology for website selection, categorization, web scraping, sentence filtering, and quantification of terms. Software package versions are indicated in parentheses.

tax-exempt organizations, either nonprofit or not-for-profit (their income is not distributed to members or officers of the organization), were assigned to a single "nonprofit" category ($n = 22$) (Supplementary Table S1). All nonprofit websites had a .org domain, except for one website, which had a .edu domain (Supplementary Table S1). For each of the 73 websites, the site type, source country, and SEMrush score (measurement of a website's popularity) were recorded (Supplementary Table S1). Sixty websites were from the US, nine were from Non-US countries, and four were international (Supplementary Table S1).

Selection of target words and phrases

We selected target words and phrases to quantify from websites that were associated with statistically significant risk factors for T2D (6, 7, 13–16) and we categorized them into three term categories: (A) dietary factors, (B) nondietary nongenetic (lifestyle-associated) factors, and (C) genetic (non-modifiable) factors (Table 1). Dietary words and phrases were further categorized into the following six subcategories: (1) sugar, (2) refined carbohydrates, (3) fiber, (4) fruits or vegetables, (5) dietary fat, and (6) red meat or processed meat (Table 1). Nondietary nongenetic (lifestyle-associated) words and phrases were further categorized into the following four subcategories: obesity, physical activity, blood pressure, dyslipidemia (Table 1). Genetic (non-modifiable) words and phrases were further categorized into three subcategories: age, family history, and ethnicity. All target words and phrases were present in at least three of the 73 websites (Table 1).

Web scraping, sentence filtering, and quantification of terms

We downloaded the hypertext from each of the 73 websites and then used a Python package, Trafilatura (version 1.3.0) (21), to extract the main text of each website. We used Python's web-automating library, Selenium (version 4.7.2) (22), to extract the complete main text from websites that dynamically load data from servers. The main text was organized into sentences using Python's built-in regular expressions library. Sentences were converted to lower-case text before searching for target words and phrases. Each sentence was searched against target words and phrases (Table 1). Sentences containing a target word or phrase were stored in a Python dictionary. Each sentence in the Python dictionary was manually checked to determine if a target word or phrase was being used in the context of causes/risk factors or preventions for T2D. For example, the sentence "Avoid sugary drinks," was recorded as providing a "sugar" term. However, the sentence "Patients with type 2 diabetes have high blood sugar levels," would be deleted from the Python dictionary, because sugar was not used in a dietary context as a cause/risk factor or prevention for T2D. A flow diagram of the above methodology is provided (Figure 1).

All the sentences that passed the manual filtering step were used to quantify per-website count of target words and phrases (Table 1); and those counts were used to determine subcategory and category usage (Table 1) among 73 websites (Table 1). The computer code that we wrote for website text extraction and quantification of target words and phrases is available on GitHub: https://github.com/MHannanAslam/Quantification-of-T2DM-risk-factors-from-websites (23).

Statistical analysis

We quantified the presence/absence (1/0) of at least one target word or phrase associated with each of the 13 subcategory terms (Table 1), per website. The presence/absence values were used to calculate the percentage of websites that used at least one target word or phrase associated with each of the 13 subcategory terms (Table 1). We took this approach because some subcategory terms, such as "sugar," have more synonymous words and phrases associated with them than other subcategory terms, and therefore, if we had quantified the total number of target words and phrases used per subcategory term, per website, it would have yielded inflated counts for subcategory terms that have a lot of synonyms.

To determine the effect of term category (dietary, nondietary nongenetic, genetic) and website type (business, government, nonprofit) on the usage of words and phrases associated with 13 subcategory terms (Table 1), among 73 websites (Supplementary Table S1), a repeated

TABLE 1 Target words and phrases that were quantified from 73 diabetes websites and their categorization for statistical analyzes.

Term Category	Term subcategory	Target words and phrases in term subcategory				
Category A: Dietary Factors	Sugar	Sugar_	Sweet_	Soda	Sucrose	
	Refined carbs	Glycemic index	Glycemic load	Processed	Refined	
	Fiber	Fiber	Whole grain /whole-grain			
	Fruit/vegetables	Fruit	Vegetables			
	Dietary fat	Saturated fat_	Unsaturated fat_	Low-fat/low fat		
	Red meat or processed meat	Red meat	Processed meat			
Category B: Nondietary Nongenetic Factors	Obesity	Obese/obesity	Weight_	Abdominal/belly fat	Body mass index/BMI	Adiposity
	Physical activity	Exercis_	Activ_	Sedentary		
	Blood pressure	Hypertension	Blood pressure			
	Dyslipidemia	Dyslipidemia	Triglyceride	Cholesterol	HDL	LDL
Category C: Genetic Factors	Age	Age_	Old_			
	Family history	History	Genetic_			
	Ethnicity	Ethnicit_				

All target words and phrases in the same row are associated with the same "term subcategory" (second column). The use of "_" after a word denotes that any word containing that root word was counted (e.g., "weight_" includes "overweight," "weight gain," "extra weight," and "healthy weight").

measures general linear model was performed in SPSS Statistics (version 28.0.1.1). In our model, the 13 subcategory terms (sugar, refined carbohydrates, fiber, fruit/vegetables, dietary fat, red meat/processed meat, obesity, physical activity, blood pressure, dyslipidemia, age, family history, ethnicity) were the subjects; the percentage of websites that provided at least one word or phrase associated with a given subcategory term (Table 1) was the response variable (repeated measure); the term category (dietary, nondietary nongenetic, genetic) was the between subjects factor; and website type (business, government, nonprofit) was the within subjects variable. A Bonferroni correction was applied to multiple pairwise comparisons of website types and term category types. Statistical significance was set to $p < 0.05$.

Results

Term category vs. percent usage of specific terms

Among the 73 websites analyzed that discussed T2D causes/risk factors and preventions, term category (dietary, nondietary nongenetic, genetic) had a significant main effect on the usage of specific terms ($p = 0.016$; Figure 2). Mean percent usage of dietary terms (26.3% ± 8.9% SE) was significantly lower ($p = 0.016$) than mean percent usage of nondietary nongenetic terms (75.7% ± 10.9% SE) and nonsignificantly lower ($p = 0.292$) than mean percent usage of genetic terms (54.4% ± 12.6% SE) (Figure 2). The mean percent usage of nondietary nongenetic terms (75.7% ± 10.9% SE) was not significantly different ($p = 0.685$) than the mean percent usage of genetic terms (54.4% ± 12.6% SE) (Figure 2).

When examining the use of specific terms among websites as causes/risk factors and preventions for T2D, obesity and physical activity were discussed in nearly all of the websites (98.6% for each term); age and family history were discussed in most websites (69.8 and 74.0% respectively); blood pressure and dyslipidemia were discussed in approximately half of the websites (56.2 and 49.3% respectively); and each of the six dietary terms were discussed in less than 40% of websites, with sugar being the most mentioned (39.7%) of the dietary terms and processed meat/red meat being the least mentioned (8.2%) (Figure 3).

Website type vs. percent usage of specific terms

Website type (business, government, nonprofit) had a significant main effect on the usage of specific terms ($p < 0.001$; Figure 4) for causes/risk factors and preventions for T2D. The mean percent usage of terms (all categories) was significantly lower among government websites (37.2% ± 9.1% SE) compared to business websites (51.5% ± 8.6% SE; $p = 0.009$) and compared to nonprofit websites (50.3% ± 6.8% SE; $p = 0.007$) (Figure 4). There was no significant difference ($p = 1.000$) in mean percent term usage between business websites (51.5% ± 8.6% SE) and nonprofit websites (50.3% ± 6.8% SE) (Figure 4). The interaction between term category x website type was not significant ($p = 0.133$) in its effect on percent term usage; meaning that the effect of term category on percent term usage was not significantly different among different website types (Figure 5).

"Healthy diet" used without mention of dietary terms

We observed the use of nonspecific dietary guidance in some websites, including "healthy diet" (27 websites), "healthy eating" (19

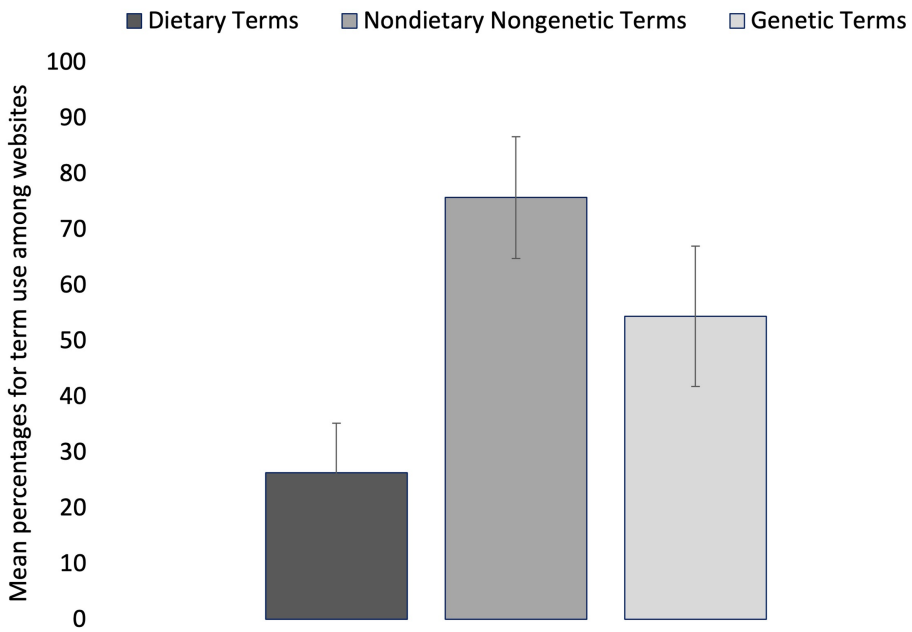

FIGURE 2
Mean percentages for term use among 73 diabetes websites. Terms are grouped into three categories: dietary, nondietary nongenetic (lifestyle-associated), and genetic (non-modifiable). Error bars represent mean standard error for the term percentages within each category.

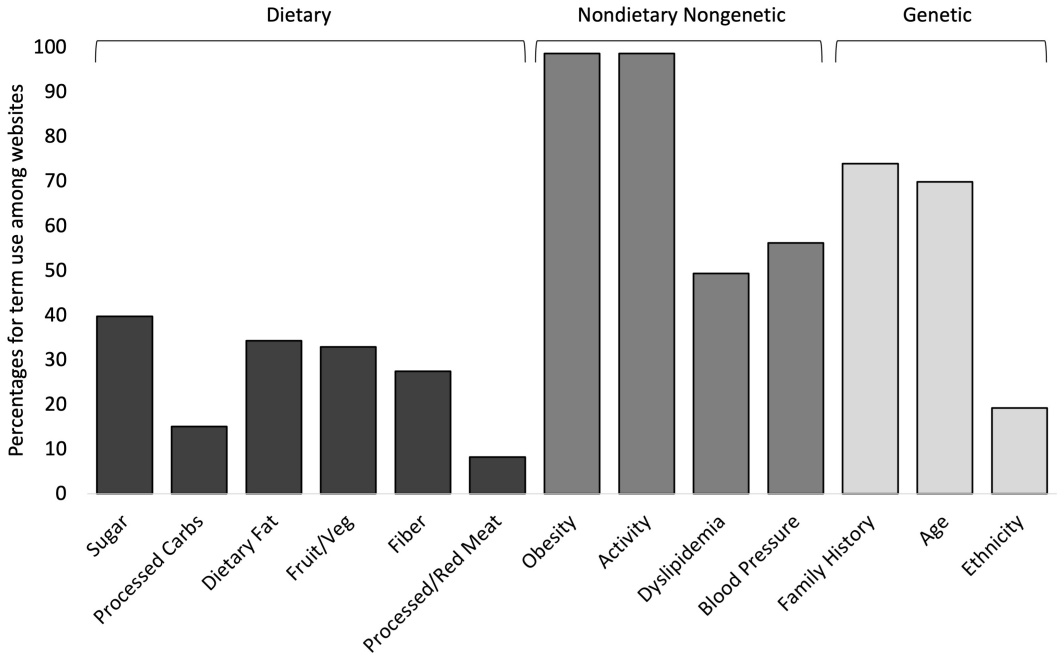

FIGURE 3
Percentages for term use among 73 diabetes websites for 13 subcategory terms. The three term categories used in statistical analyzes are shown above the brackets at the top of the figure.

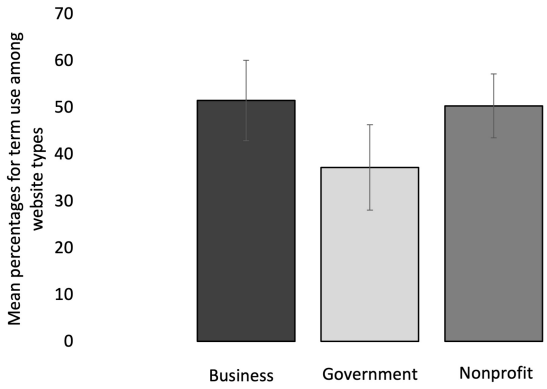

FIGURE 4
Mean percentages for term use (all term categories included) among 73 diabetes websites that are grouped into three type categories: business, government, and nonprofit. Error bars represent mean standard error for the term percentages within each website category.

websites), "eat healthy" (12 websites), and "balanced diet" (4 websites), but in many cases, no specific dietary terms (sugar, processed carbs, fiber, etc.) that are associated with significant causes/risk factors and preventions for T2D were provided in addition to the nonspecific dietary guidance. Among the 47 websites that provided some form of nonspecific dietary guidance, 32% did not provide any dietary terms associated with significant causes/risk factors and preventions for T2D, 19% provided only one dietary term, and 19% provided only two specific dietary terms (Figure 6). Thus, only 30% of the websites providing "eat healthy" advice for causes/risk factors and preventions for T2D, also provided more than two specific dietary terms with the advice (Figure 6).

Discussion

Significance of findings

To our knowledge, a systematic review of causes/risk factors and preventions for T2D in the gray literature (websites) has not been performed until now. There is a great need for this type of review because of the growing prevalence of T2D around the world and the need for accurate information about T2D prevention to be accessible to everyone. An unexpected finding was that government websites, comprised of mostly state and federal government agencies (88%), provided significantly fewer causes/risk factors and preventions for T2D, from all categories, than either business websites or nonprofit websites. This suggests that government agencies need to invest more effort into ensuring that the health information provided in their diabetes websites is up-to-date, informative, and effective in disease prevention. We were also surprised to find that many of the websites that provide "eat healthy" guidance in association with causes/risk factors and preventions for T2D, provided little to no specific dietary guidance, such as: limit intake of added sugars (13–16), increase intake of polyunsaturated fats (16, 24, 25), increase intake of high-fiber foods (14–16, 26, 27). Without such dietary guidance, phrases like "eat healthy" are not useful in educating the public on how to prevent T2D. Since we only examined websites written in English, our findings cannot be extrapolated to diabetes websites written in other languages and we encourage others to conduct similar studies of diabetes websites

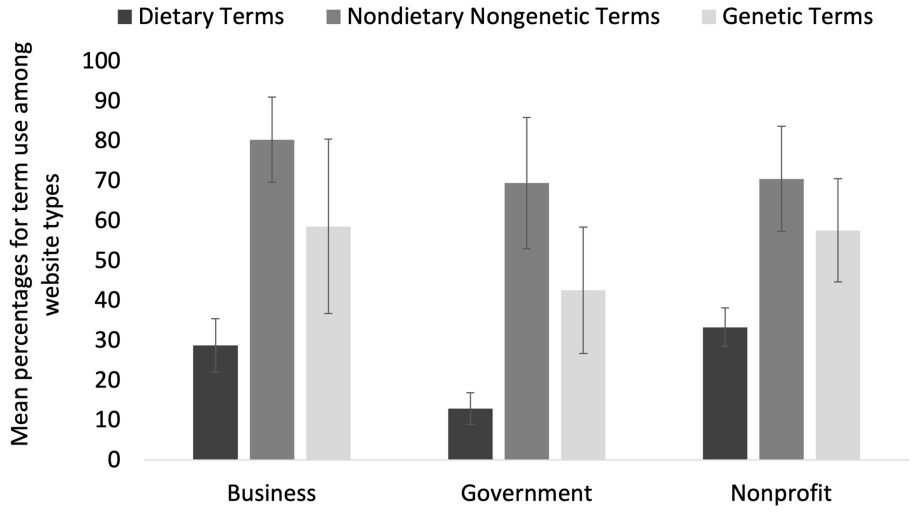

FIGURE 5
Mean percentages for term use among 73 websites, where terms are grouped into three subcategories: dietary, nondietary nongenetic (lifestyle-associated), and genetic (non-modifiable) and websites are grouped into three type categories: business, government, and nonprofit. Error bars represent mean standard error for the term percentages within each category.

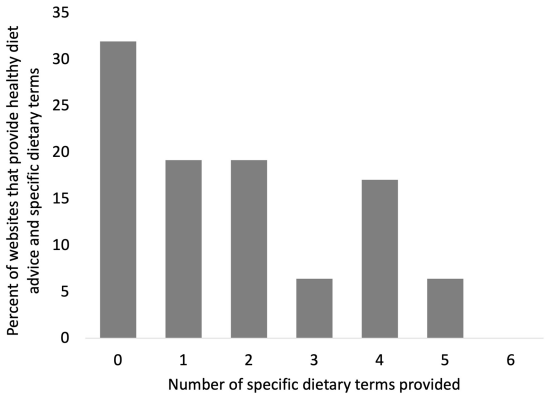

FIGURE 6
Of the 47 diabetes websites that provide "healthy diet advice," this is the percentage of websites that provide a given number of dietary terms. The total number of dietary terms quantified from diabetes websites was six.

written in non-English languages. Overall, our findings demonstrate a paucity of information on diabetes websites regarding dietary causes/risk factors, and preventions for T2D. This lack of dietary information is problematic for several reasons, which we will discuss below.

Why exclusion of dietary risk factors and preventions for T2D is problematic

All four of the nondietary nongenetic (lifestyle-associated) risk factors for T2D (obesity, physical activity, dyslipidemia, and high blood pressure) are significantly associated with dietary factors, which may be their ultimate cause. An example of a strong association between a dietary risk factor and multiple nondietary nongenetic (lifestyle-associated) risk factors, is found with sugar. In addition to promoting insulin resistance (28–30), high sugar and/or fructose intake has been shown to promote dyslipidemia and increase fat storage (31–33), increase visceral adiposity (28, 33, 34), and cause leptin resistance (33, 35, 36), which is associated with (1) an increased drive to consume excessive amounts of energy (37) and (2) a reduction in energy expenditure (associated with lethargy) (32, 38). Further, many studies have shown that high sugar intake, particularly the fructose component of sugar, promotes hypertension (39–42), *via* stimulation of the sympathetic nervous system. This illustrates how a dietary risk factor for T2D is strongly associated with all the nondietary nongenetic risk factors: obesity, physical activity, dyslipidemia, and blood pressure; and thus, should be included.

When discussing obesity in association with T2D, it is important to point out that certain dietary factors promote an increase in different types of body fat, and not all body fat is associated with T2D. Subcutaneous fat is not a significant predictor of T2D whereas visceral fat (aka central or abdominal fat) is the strongest predictor of insulin resistance and T2D incidence (43–47). There are significant dietary associations with visceral fat. Overfeeding normal individuals with saturated fat resulted in a two-fold higher increase in visceral fat (the dangerous fat), compared to overfeeding with polyunsaturated fats (48). Studies also show that replacing saturated fat with polyunsaturated fats significantly improves insulin sensitivity (24, 25). Excess fructose intake has been shown to significantly increase visceral fat, but not subcutaneous fat, and significantly decreases insulin sensitivity (28). Alternately, excess glucose intake significantly increases subcutaneous fat, but not visceral fat, and does not affect insulin sensitivity (28). Similarly, when sugar (fructose + glucose) was replaced with starch (glucose) in children with obesity and metabolic syndrome, their glucose tolerance significantly improved

in just nine days, along with their blood pressure, triglycerides, and insulin levels (30). Thus, information regarding specific dietary modifications, particularly reduced intake of added sugars and replacement of saturated fats with polyunsaturated fats, is important for reducing visceral adiposity and associated T2D risk.

Among lifestyle factors that can be modified to prevent the development of T2D, modification of dietary factors, alone, may be just as effective at reducing T2D risk as increasing physical activity, alone. A recent meta-analysis of randomized controlled trials and observational studies examining dietary factors and T2D risk, reported that dietary interventions, with or without physical activity, significantly decreased T2D risk in both high risk populations and the general population (16). People with T2D who changed their diet to a paleolithic diet over 12 weeks, showed significant improvement in glycemic control and insulin sensitivity; and the improvement was not significantly different than participants who underwent an exercise intervention + dietary intervention (49). Other intervention studies reported similar findings, in that diet + exercise intervention did not show greater improvement of glycemic control and insulin sensitivity than diet intervention alone (50, 51). For all the reasons that we have discussed, diabetes websites should make a concerted effort to include significant dietary factors when discussing T2D causes/risk factors and preventions to better educate the public on how to prevent the development of T2D.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

LC conceptualized the study and designed the methodology, performed data curation, statistical analysis, and interpretation of the data, and prepared the first draft. MA wrote computer code for data extraction and performed data curation. MA and LC revised subsequent drafts and read and approved the final manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1159024/full#supplementary-material

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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 21 September 2023
DOI 10.3389/fendo.2023.1180910

OPEN ACCESS

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RECEIVED 06 March 2023
ACCEPTED 04 September 2023
PUBLISHED 21 September 2023

CITATION
Song B, Wang K, Lu W, Zhao X, Yao T, Liu T, Gao G, Fan H and Liu C (2023) A U-shaped association between the triglyceride to high-density lipoprotein cholesterol ratio and the risk of incident type 2 diabetes mellitus in Japanese men with normal glycemic levels: a population-based longitudinal cohort study. *Front. Endocrinol.* 14:1180910. doi: 10.3389/fendo.2023.1180910

A U-shaped association between the triglyceride to high-density lipoprotein cholesterol ratio and the risk of incident type 2 diabetes mellitus in Japanese men with normal glycemic levels: a population-based longitudinal cohort study

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Background: Several studies have verified that a high baseline TG/HDL-C ratio is a risk factor for incident type 2 diabetes mellitus (T2DM). However, for low baseline TG/HDL-C levels, the findings were inconsistent with ours. In addition, the association between baseline TG/HDL-C ratio and the risk of incident T2DM in Japanese men with normal glycemic levels is unclear. As a result, our study further investigated the relationship between baseline TG/HDL-C and the risk of incident T2DM in Japanese men with normal glycemic levels.

Methods: This was a secondary longitudinal cohort study. We selected 7,684 male participants between 2004 and 2015 from the NAGALA database. A standardized Cox regression model and two piecewise Cox regression models were used to explore the relationship between the baseline high-density lipoprotein cholesterol ratio (TG/HDL-C) and incident T2DM.

Results: During a median follow-up of 2,282 days, 162 men developed incident T2DM. In the adjusted model, the baseline TG/HDL-C ratio was strongly associated with the risk of incident T2DM, and no dose-dependent positive association was observed between the baseline TG/HDL-C ratio and incidence of T2DM throughout the baseline TG/HDL-C quartiles. Two-piecewise linear regression analysis showed a U-shaped association between baseline TG/HDL-C ratio and incidence of incident T2DM. A baseline TG/HDL-C ratio below 1.188 was negatively associated with incident T2DM (H.R. = 0.105, 95% CI = 0.025, 0.451; P = 0.002). In contrast, a baseline TG/HDL-C ratio >1.188 was positively associated with incident T2DM (H.R. = 1.248, 95% CI = 1.113, 1.399; P<0.001). The

best TG/HDL-C threshold for predicting incident T2DM was 1.8115 (area under the curve, 0.6837).

Conclusion: A U-shaped relationship between baseline TG/HDL-C ratio and incident T2DM in Japanese men with normal glycemic levels was found.

KEYWORDS

triglyceride to high-density lipoprotein cholesterol ratio, type 2 diabetes mellitus, cohort study, normal glycemic level, Japanese men

1 Introduction

Diabetes is one of the most common chronic metabolic diseases (1). Diabetes has been identified by the International Diabetes Federation (IDF) as one of the fastest-growing global health emergencies of the 21st century with a profound economic impact. In 2021, there were approximately 537 million people with diabetes worldwide, and approximately 643 million people will have diabetes by 2030, and 783 million by 2045. The number of people with diabetes is increasing in Japan. In 2021, Japanese adults had the world's fifth highest health spending on diabetes, at approximately 35.6 billion dollars. Type 2 diabetes mellitus (T2DM), is the most common form of diabetes, accounting for 90% of all cases (2). Therefore, the prevention and early diagnosis of type 2 diabetes are crucial.

In the pathogenesis of T2DM, insulin resistance (IR) plays an important role (3). Lipid metabolism disorders are the main cause of IR pathophysiology (4). High levels of triglycerides (TG) and low levels of high-density lipoprotein cholesterol (HDL-C) are closely associated with IR and T2DM (5). TG/HDL-C is closely related to IR according to previous studies, which has been advocated as a simple clinical indicator of IR (6, 7). Three studies based on Chinese populations and one study based on Singapore Chinese men and women consistently found that triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio was positively associated with the risk of T2DM (8–11). A dose-dependent relationship between TG/HDL-C ratio and the risk of incident T2DM was also found in a study of Korean adults (12). However, one study in Iran showed that TG/HDL-C ratio was not associated with the risk of incident T2DM (13). However, in a Chinese population-based study, a stronger association between TG/HDL-C and incident diabetes mellitus was found in people with baseline fasting plasma glucose (FPG) of less than 6.1 mmol/L, which indicates that our study should further investigate the relationship between TG/HDL-C and incident T2DM in individuals with FPG less than 6.1 mmol/L (14). We only included participants with fasting blood glucose less than 6.1 mmol/L and HbA1c less than 5.7% at baseline to exclude people with prediabetes at baseline. The most important finding was that our study found a specific U-shaped relationship between TG/HDL-C and the risk of incident T2DM in Japanese men which was completely different from previous studies in other countries.

Our study was a population-based cohort study to examine the association between TG/HDL-C ratio and the risk of incident T2DM in Japanese men aged 18–69 years. Women were excluded because we found an interesting U-shaped relationship between TG/HDL-C and the risk of incident T2DM among Japanese men but not among Japanese women. We hope that our study will contribute to the diagnosis and prevention of incident T2DM in Japanese men and provide a basis for future clinical and mechanistic studies.

2 Methods and materials

2.1 Participants

In this study, we used data from the NAGALA (NAFLD in the Gifu Area, Japan, Longitudinal Analysis) database to conduct a secondary analysis. Between 2004 and 2015, these data were obtained from the Murakami Memorial Hospital Examination Project. A total of 12,498 men and 8,446 women were enrolled in this study. However, because our analysis found a unique threshold effect between TG/HDL-C ratio and incident T2DM in Japanese men with normal glycemic levels, we included only 12,498 men. Furthermore, we excluded participants who had liver disease (e.g., alcoholic fatty liver disease and viral hepatitis), any medication usage, and excessive drinking habits at baseline. Participants who lacked covariates such as height, TG/HDL-C ratio, exercise habits, alcohol consumption, or abdominal ultrasonography were also excluded. Finally, we only included participants with fasting blood glucose less than 6.1 mmol/L and HbA1c less than 5.7% at baseline, because we wanted to exclude people with prediabetes at baseline. The study was approved by the Murakami Memorial Hospital Ethics Committee, and the participants signed written informed consent forms.

2.2 Data collection and measurements

Data were collected using a self-report questionnaire that included information about the participants' lifestyle (alcohol and smoking habits and physical activity) and history of drug use. Alcohol consumption, defined as the average weekly alcohol

intake, was estimated by asking participants about their average weekly alcohol intake in the month prior to the examination. To facilitate statistical analysis, four groups were formed as follows: non-drinker,<40 g/week; light drinker, 40 g/week–140 g/week; moderate drinker, 140 g/week–280 g/week; and severe drinker, >280 g/week. Three groups were formed based on smoking status: never smokers (never smoked), former smokers (previously smoked but quit before the baseline examination), and current smokers (during the baseline examination, he smoked). Exercise habits were defined as participation in exercise once a week or more regularly. In the original data, fatty liver was diagnosed mainly using abdominal ultrasonography. The gastroenterologist diagnosed the participants with fatty liver based on liver brightness and contrast. Hepatitis B antigen and hepatitis C antibody-positive patients were defined as those with viral hepatitis. T2DM was described as HbA1c greater than or equal to 6.5%and fasting blood glucose greater than or equal to 7 mmol/L after physical examination at follow-up or as self-reported by the participants. However, because the oral glucose tolerance test (OGTT) was not performed during diagnosis, the incidence rate of T2DM may be underestimated.

2.3 Definition of TG/HDL-C

$$\mathrm{TG/HDL-C} = \text{triglyceride (mmol/L)/high-density lipoprotein cholesterol(mmol/L)}$$

2.4 Statistical analysis

All statistical analyses in our study used the statistical packages R and EmpowerStats (15). As shown in Table 1, the TG/HDL-C ratio was divided into four groups (Q1–Q4). To make the analysis results more reliable and accurate, we divided the participants into four equal groups based on the TG/HDL-C ratio. Continuous variables were expressed as mean ± standard deviation (SD). The Kolmogorov–Smirnov test was used to assess the normality of the data, and the Student's t-test was used to assess statistical differences between groups for continuously normally distributed variables. If the normality assumption was not met, the Mann–Whitney U test was used for statistical analysis. Categorical data were expressed as frequencies (percentages). Statistical differences between categorical variables were analyzed using the chi-squared test. We performed Cox regression analysis to assess the independent effect of the baseline TG/HDL-C ratio on the incidence of T2DM (Table 2). We used four models: (1) a crude model without adjustment. (2) Model I adjusted for age and BMI. (3) Model II adjusted for age, BMI, fatty liver, waist circumference, body weight, alcohol consumption, smoking status, exercise habits, systolic blood pressure, and diastolic blood pressure. (4) Model III was adjusted for all variables with P<0.001 in the univariate analysis (baseline age, BMI, fatty liver, waist circumference, body weight, alcohol consumption, smoking status, exercise habits, systolic blood pressure, diastolic blood pressure, total cholesterol, HbA1c, fasting plasma glucose, GGT, ALT, and AST) (Supplementary Table 1). Finally, in Table 3, we used a two-piecewise linear regression model to examine the threshold effect of the baseline TG/HDL-C ratio on incident T2DM, which was in terms of the smoothing plot (Figure 1). We used the maximum likelihood model to further calculate the inflection points. In Figure 2 and Table 4, receiver operating characteristic (ROC) curve analysis was used to calculate the area under the curve (AUC) and the best threshold, which showed the predictive value of the TG/HDL-C, TG, and HDL-C for incident T2DM risk.

3 Results

3.1 Study population description based on TG/HDL-C quartiles

A total of 12,498 men and 8,446 women were initially enrolled in the NAGALA cohort study. However, because our analysis found a unique threshold effect between incident T2DM and TG/HDL-C ratio in Japanese men with normal glycemic levels, we included only 12,498 men. Furthermore, 788 men were excluded due to a lack of covariates, such as height, TG/HDL-C, exercise habits, alcohol consumption, or abdominal ultrasonography. The 2,622 men who had liver disease, medication usage, and excessive drinking habits at baseline were also excluded. A total of 677 men were also excluded, including 265 with type 2 diabetes at baseline and 667 with fasting blood glucose of more than 6.1 mmol/L or HbA1c >5.7% at baseline. Therefore, 7,684 men were included in this cohort study (Figure 3).

The baseline characteristics of the study participants are shown in Table 1. In our cohort, the mean age was 43.80 ± 8.90 years. At a mean follow-up of 2,281.59 ± 1,411.46 days, 162 (2.11%) subjects developed incident T2DM. All baseline variables showed statistically significant differences between the quartiles. Participants in the higher TG/HDL-C quartiles were more likely to be incident T2DM patients, older, fatty liver patients, current smokers, non-drinkers, severe drinkers, persons who had no exercise habits, and had higher body weight, BMI, triglycerides, total cholesterol, fasting plasma glucose, ALT, AST, GGT, HbA1c, systolic blood pressure, diastolic blood pressure, larger waist circumference, but less likely to be light drinkers, moderate drinkers, non-smokers, past smokers, and those with lower HDL-cholesterol levels (P<0.001).

3.2 The association between incident T2DM and baseline TG/HDL-C

We performed Cox regression analysis to assess the independent effect of the baseline TG/HDL-C ratio on the incidence of T2DM (Table 2). In the crude model, the risk of T2DM was prominently associated with baseline TG/HDL-C in men (P<0.001). In Model I, the association remained significant after adjusting for age and BMI. In addition, Model II was further adjusted for waist circumference, body weight, fatty liver, alcohol consumption, smoking status, systolic blood pressure, diastolic blood pressure, and exercise habits, which did not

TABLE 1 Baseline variables according to the quartile of TG/HDL-C.

Variable	TG/HDL-C				*P*-value
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
	(0.1448–0.9978)	(1.0000–1.5957)	(1.5960–2.6075)	(2.6078–6.7895)	
N	1,900	1,942	1,921	1,921	
Case of Incident T2DM	19 (1.00%)	18 (0.93%)	45 (2.34%)	80 (4.16%)	<0.001
Age, yr	42.41 ± 9.10	43.83 ± 9.11	44.23 ± 8.83	44.71 ± 8.40	<0.001
Body Weight, kg	62.97 ± 8.27	65.24 ± 8.83	68.04 ± 9.88	71.34 ± 9.82	<0.001
Waist circumference, cm	75.69 ± 6.70	78.66 ± 6.94	81.49 ± 7.53	84.40 ± 7.19	<0.001
BMI, kg/m^2	21.45 ± 2.43	22.35 ± 2.59	23.30 ± 2.89	24.44 ± 2.82	<0.001
HDL-C, mmol/L	1.65 ± 0.36	1.38 ± 0.25	1.22 ± 0.21	1.06 ± 0.19	<0.001
TG, mmol/L	0.49 ± 0.14	0.76 ± 0.16	1.08 ± 0.22	1.76 ± 0.47	<0.001
Total cholesterol, mmol/L	4.86 ± 0.79	5.00 ± 0.79	5.20 ± 0.81	5.45 ± 0.86	<0.001
ALT, IU/L	19.13 ± 9.83	21.20 ± 10.69	24.20 ± 13.21	28.75 ± 16.55	<0.001
AST, IU/L	18.73 ± 7.88	18.63 ± 6.52	19.29 ± 6.95	21.05 ± 8.62	<0.001
GGT, IU/L	20.07 ± 15.10	22.80 ± 16.82	26.08 ± 21.67	31.15 ± 24.63	<0.001
HbA1c, %	5.14 ± 0.30	5.15 ± 0.31	5.18 ± 0.33	5.21 ± 0.34	<0.001
Fasting plasma glucose, mmol/L	5.21 ± 0.37	5.26 ± 0.35	5.30 ± 0.35	5.36 ± 0.36	<0.001
Systolic blood pressure, mmHg	115.16 ± 13.06	117.65 ± 13.51	118.95 ± 14.12	121.87 ± 14.45	<0.001
Diastolic blood pressure, mmHg	71.90 ± 9.61	74.06 ± 9.36	75.03 ± 9.78	77.30 ± 10.01	<0.001
Follow-up duration, days	2,041.83 ± 1,358.25	2,307.72 ± 1,422.34	2,348.04 ± 1,413.71	2,425.88 ± 1,421.53	<0.001
Fatty liver					<0.001
No	1,770 (93.16%)	1,646 (84.76%)	1,390 (72.36%)	1,033 (53.77%)	
Yes	130 (6.84%)	296 (15.24%)	531 (27.64%)	888 (46.23%)	
Habit of exercise					<0.001
No	1,427 (75.11%)	1,551 (79.87%)	1,577 (82.09%)	1,641 (85.42%)	
Yes	473 (24.89%)	391 (20.13%)	344 (17.91%)	280 (14.58%)	
Alcohol consumption					0.037
Never	1,166 (61.37%)	1,194 (61.48%)	1,228 (63.93%)	1,259 (65.54%)	
Light	329 (17.32%)	348 (17.92%)	306 (15.93%)	276 (14.37%)	
Moderate	287 (15.11%)	270 (13.90%)	273 (14.21%)	250 (13.01%)	
Severe	118 (6.21%)	130 (6.69%)	114 (5.93%)	136 (7.08%)	
Smoking status					<0.001
Never	815 (42.89%)	678 (34.91%)	604 (31.44%)	598 (31.13%)	
Past	573 (30.16%)	612 (31.51%)	566 (29.46%)	529 (27.54%)	
Current	512 (26.95%)	652 (33.57%)	751 (39.09%)	794 (41.33%)	

Continuous variables are presented as mean ± S.D. or as median (Q1–Q4). Categorical data are presented as frequencies (percentages).
Q, quartile; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; DBP, diastolic blood pressure; SBP, systolic blood pressure; HDL-C, high-density lipoprotein-cholesterol; TG, triglyceride; TG/HDL-C, triglyceride to high-density lipoprotein cholesterol ratio; HbA1c, Hemoglobin A1c; BMI, body mass index.

alter the significant association among men (P<0.001), but it was weaker than Model I. Model III adjusted for all variables (baseline age, waist circumference, body weight, fatty liver, BMI, alcohol consumption, exercise habits, smoking status, diastolic blood pressure, systolic blood pressure, total cholesterol, AST, ALT, and GGT) associated with incident T2DM in univariate analysis, and significant correlations remained (P<0.05) (Supplemental Table 1). We then divided the participants into four groups based on the baseline TG/HDL-C ratio.

TABLE 2 Associations of baseline TG/HDL-C with incident T2DM.

	Incident T2DM			
	Crude Model	Model I	Model II	Model III
	H.R. (95%CI) *P*-value	H.R. (95%CI) *P*-value	H.R. (95%CI) *P*-value	H.R. (95%CI) *P*-value
TG/HDL-C continuous	**1.469 (1.340, 1.610)<0.001**	**1.301 (1.175, 1.440)<0.001**	**1.196 (1.073, 1.332) 0.001**	**1.188 (1.063, 1.327) 0.002**
TG/HDL-C quartile				
Q1	**1.000**	**1.000**	**1.000**	**1.000**
Q2	**0.755 (0.396, 1.439) 0.393**	**0.597 (0.313, 1.141) 0.118**	**0.490 (0.255, 0.941) 0.032**	**0.486 (0.253, 0.936) 0.031**
Q3	**1.872 (1.095, 3.201) 0.022**	**1.214 (0.701, 2.102) 0.488**	**0.910 (0.520, 1.593) 0.741**	**0.891 (0.505, 1.573) 0.692**
Q4	**3.151 (1.910, 5.199)<0.001**	**1.619 (0.961, 2.727) 0.070**	**1.050 (0.609, 1.810) 0.861**	**1.012 (0.578, 1.773) 0.967**

Crude model adjusted for None.
Model I adjusted for baseline age and BMI.
Model II adjusted for baseline age, BMI, fatty liver, waist circumference, body weight, exercise habits, alcohol consumption, smoking status, systolic blood pressure, and diastolic blood pressure.
Model III adjusted for baseline age, fatty liver, BMI, waist circumference, body weight, exercise habits, alcohol consumption, smoking status, systolic blood pressure, diastolic blood pressure, total cholesterol, GGT, ALT, and AST.
HR, hazard ratio; CI, confidence intervals; Q, quartile; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; DBP, diastolic blood pressure; SBP, systolic blood pressure; HDL-cholesterol, high-density lipoprotein-cholesterol; TG/HDL-C, triglyceride to high-density lipoprotein cholesterol ratio; BMI, body mass index.

Neither model showed a dose-dependent positive relationship between the baseline TG/HDL-C quartile and the risk of T2DM. In Model III Compared to the TG/HDL-C quartile 1, the risk of incident T2DM did not increase significantly in quartiles 2 (HR = 0.443, 95% CI = 0.229, 0.856; P = 0.015), 3 (HR = 0.841, 95% CI = 0.478, 1.479; P = 0.548), and 4 (HR = 0. 0.848, 95% CI = 0.487, 1.478; P = 0.561) of TG/HDL-C. These findings illustrate the significant nonlinear relationship between baseline TG/HDL-C ratio and incident T2DM.

3.3 Two piecewise linear regression analysis and threshold effect analysis of TG/HDL-C on the Incident T2DM

Because previous multiple regression analyses indicated a nonlinear association between baseline TG/HDL-C ratio and the risk of incident T2DM, a threshold effect analysis with a smooth function was used to further clarify the association. Interestingly, smooth curves adjusted for multiple confounders showed a U-shaped association between TG/HDL-C ratio and the risk of T2DM in Japanese men (Figure 1). According to the two piecewise linear regression models, after adjusting for confounding variables, the baseline TG/HDL-C ratio was negatively correlated with the log-relative risk of incident T2DM when the baseline TG/HDL-C ratio was less than 1.188. After adjusting for baseline age, waist circumference, body weight, fatty liver, BMI, alcohol consumption, exercise habits, smoking status, diastolic blood pressure, systolic blood pressure, total cholesterol, AST, ALT, and GGT when TG/HDL-C ratio was less than 1.188, the risk of incident T2DM in Japanese men decreased by nearly 89.5% for each unit increase in TG/HDL-C ratio (HR = 0.105, 95% CI = 0.025, 0.451; P = 0.002). In contrast, a baseline TG/HDL-C ratio >1.188 was significantly positively associated with the risk of T2DM (HR = 1.248, 95% CI = 1.113, 1.399; P<0.001) (Table 3).

3.4 Predictive value of TG/HDL-C in incident T2DM

To compare the predictive value of TG/HDL-C with that of TG and HDL-C, an ROC curve was drawn, and the area under the curve (AUC) was calculated. The area under the curve (AUC) of TG/HDL-C was 0.6837 (0.6397, 0.7277), which was larger than that of TG and HDL-C (Figure 2). The best threshold, specificity, and sensitivity of TG/HDL-C ratio were 1.8115, 0.575, and 0.7469, respectively (Table 4).

TABLE 3 Threshold effect analysis of baseline TG/HDL-C ratio and incident T2DM using piece-wise linear regression.

	Incident T2DM					
	Crude model		Model I		Model II	
	HR (95%CI)	*P*-value	H.R. (95%CI)	*P*-value	H.R. (95%CI)	*P*-value
TG/HDL-C<1.188	**0.791 (0.294, 2.126)**	**0.642**	**0.280 (0.101, 0.778)**	**0.015**	**0.105 (0.025, 0.451)**	**0.002**
TG/HDL-C >1.188	**1.514 (1.365, 1.679)**	**<0.001**	**1.297 (1.158, 1.454)**	**<0.001**	**1.248 (1.113, 1.399)**	**<0.001**
Likelihood ratio test *p*		**0.235**		**0.009**		**0.003**

Crude model adjusted for None.
Model I was adjusted for baseline age, fatty liver, BMI, waist circumference, and body weight.
Model II was adjusted for baseline age, fatty liver, BMI, waist circumference, ALT, AST, body weight, exercise habits, GGT, total cholesterol, alcohol consumption, smoking status, systolic blood pressure, and diastolic blood pressure.
HR, hazard ratio; CI, confidence interval; TG/HDL-C, triglyceride to high-density lipoprotein cholesterol ratio.

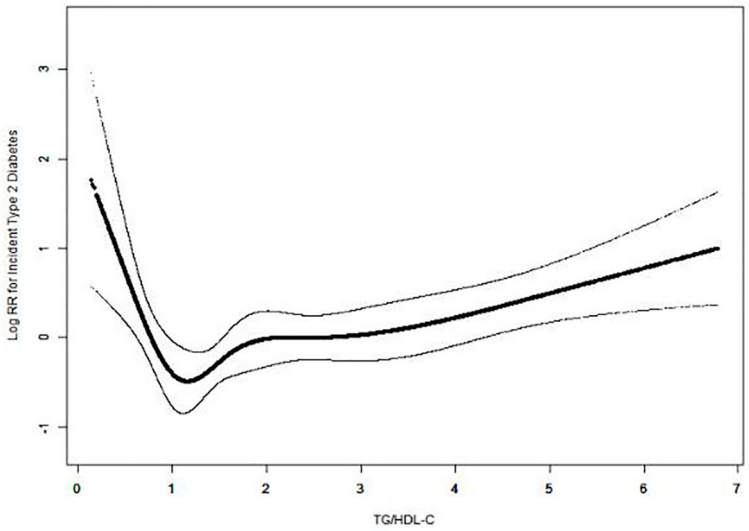

FIGURE 1
U-shaped association between TG/HDL-C ratio and incident T2DM. A nonlinear association between TG/HDL-C ratio and incident T2DM was observed in a generalized additive model (GAM). The solid black line represents the smooth curve fit between the TG/HDL-C ratio and the incidence of diabetes. Dotted curves represent 95% CI of the fit. All were adjusted for age, fatty liver, body weight, waist circumference, BMI, total cholesterol, ALT, AST, GGT, systolic blood pressure, diastolic blood pressure, alcohol consumption, smoking status, and exercise habits.

4 Discussion

4.1 Comparisons with other studies and what does the current work add to the existing knowledge

To our knowledge, our study is the first to describe a U-shaped association between baseline TG/HDL-C ratio and the risk of incident T2DM in Japanese men with normal glycemic levels. In addition, we identified a turning point (TG/HDL-C ratio = 1.188) using threshold effect analysis and a two-piecewise linear regression model. According to the two-piecewise linear regression model, when the TG/HDL-C ratio was greater than 1.188, the risk of T2DM increased significantly with an increase in baseline TG/HDL-C ratio, which was consistent with previous studies in other countries. Cheng et al. found that the incidence of T2DM increased with an increase in TG/HDL-C ratio in rural China (9). Another retrospective cohort study based on a Chinese population showed that participants with TG/HDL-C in quartiles 2, 3, and 4 had a higher risk of developing T2DM than those in quartile 1 (8).

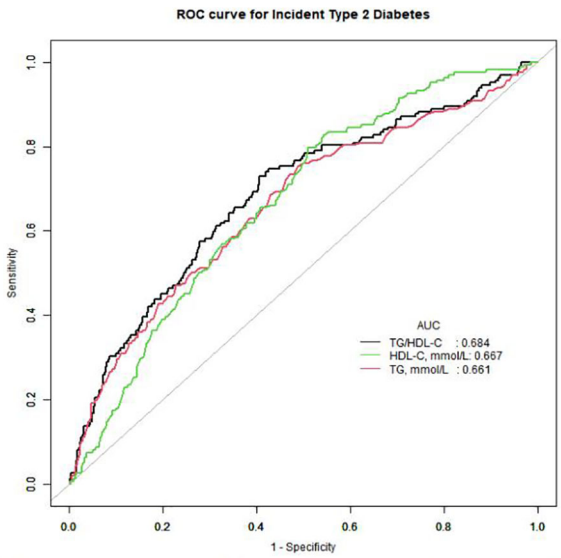

FIGURE 2
Receiver operating characteristic (ROC) curve analyses to predict incident T2DM. AUC, area under the curve; TG, triglyceride; HDL-cholesterol, high-density lipoprotein-cholesterol; TG/HDL-C, triglyceride to high-density lipoprotein cholesterol ratio.

TABLE 4 AUC with the 95% CI of TG/HDL-C, HDL-C and TG for predicting incident T2DM.

Test	ROC area (AUC)	95%CI low	95%CI up	Best threshold	Specificity	Sensitivity
TG/HDL-C	0.6837	0.6397	0.7277	1.8115	0.575	0.7469
TG	0.6611	0.6158	0.7064	0.8976	0.511	0.7531
HDL-C	0.6674	0.6298	0.705	1.2891	0.49	0.7963

AUC, area under the curve; CI, confidence interval; TG, triglyceride; HDL-cholesterol, high-density lipoprotein-cholesterol; TG/HDL-C, triglyceride to high-density lipoprotein cholesterol ratio.

However, Incident T2DM decreased in quartile 2 compared to quartile 1, which verified that there was a nonlinear relationship (U-shaped) between TG/HDL-C ratio and incident T2DM. At the same time, the results supported that when TG/HDL-C ratio was less than 1.188, it had a protective effect on new-onset type 2 diabetes in Japanese men.

This was a population-based cohort study to examine the association between TG/HDL-C ratio and the risk of incident T2DM in Japanese men aged 18-69–years. Interestingly, we found that a lower baseline TG/HDL-C ratio (TG/HDL-C<1.188) significantly altered the association between TG/HDL ratio and incident T2DM risk. After adjusting for confounding factors such as baseline age, fatty liver, BMI, waist circumference, ALT, AST, body weight, exercise habits, GGT, total cholesterol, HbA1c, alcohol consumption, smoking status, fasting plasma glucose, systolic blood pressure, and diastolic blood pressure, for each unit increase in baseline TG/HDL-C below the threshold, the risk of developing incident T2DM in Japanese men was decreased by nearly 89.5%. This result was inconsistent with those of studies conducted in China, South Korea, Singaporean Chinese, and Iran. Among them, TG/HDL-C ratio was not associated with diabetes incidence in the Iranian population (13). In addition, studies in other countries reported an increased risk of diabetes or T2DM in all TG/HDL-C groups (8–12, 14). However, most studies in these countries only excluded participants with baseline FPG greater than 7 mmol/L and did not exclude people with prediabetes (HbA1c greater than 5.7% and FPG greater than 6.1 mmol/L) (9, 12, 14). Some studies did not specify the specific criteria for the inclusion of the population or diagnosis of T2DM (8). In addition, the TG/HDL-C range in our study was wider than that in these three studies, which may partly account for the divergent results, possibly because some participants with prediabetes were included in these studies. In three studies on the Chinese population, a nonlinear relationship was found after adjusting for confounding factors (8, 9, 14). The risk of T2DM increased significantly only in quartile 4 of TG/HDL-C, but not in quartiles 2 and 3, compared with quartile 1. In addition, a study of Singapore Chinese and Korean adults did not conduct bilinear regression and smooth function analysis, and they were grouped into three groups, so specific trends could not be observed (10, 12). In conclusion, a U-shaped association between baseline TG/HDL-C ratio and the development of incident T2DM was found in Japanese men with normoglycemic levels, possibly due to different regions, different population screening patterns, and a broader range of baseline TG/HDL-C ratio.

This study has several important clinical implications. First, the association between higher TG/HDL-C ratio and the risk of incident T2DM may be due to insulin resistance. The specific mechanism remains unclear, but some studies have shown that dyslipidemia is a vital pathogenesis of insulin resistance (4). Lipotoxicity, endoplasmic reticulum (ER) stress, and inflammation are the widely accepted mechanisms for inducing IR (3, 16). Previous studies have shown that hypertriglyceridemia and low HDL-C levels are more prevalent in T2DM patients than in the normal population. In contrast, high LDL-C levels were not significantly different between the two groups (17). It has also been shown that high TG levels can cause overload of free fatty acids or

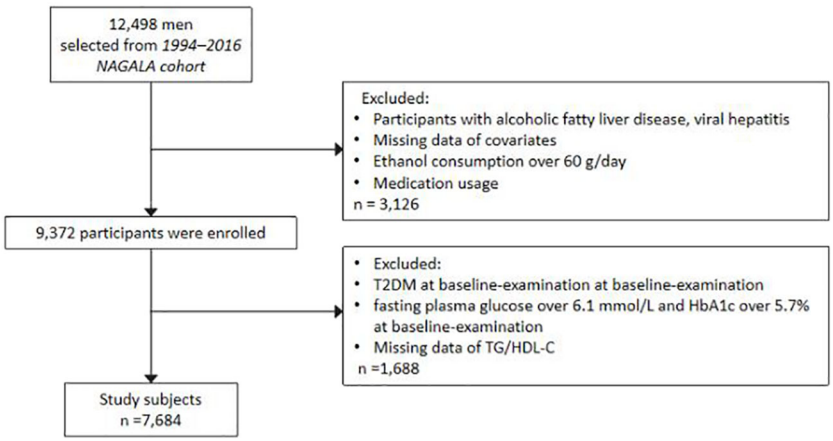

FIGURE 3
Flow chart showing the exclusion criteria of participants. NAGALA, NAfld in Gifu Area, Longitudinal Analysis; T2DM, type 2 diabetes mellitus; TG/HDL-C, triglyceride to high-density lipoprotein cholesterol ratio.

lipotoxicity in some organs, and lead to β-cell dysfunction and insulin resistance. At the same time, high TG levels can directly promote inflammatory response or ER stress (18). However, dyslipidemia may also be a direct cause of IR in the absence of lipotoxicity, such as inflammation, ER stress, or other mechanisms (5). In addition, low HDL-C levels may affect glucose homeostasis through direct glucose uptake, reducing insulin sensitivity and insulin secretion (19). Second, low TG/HDL-C levels were associated with an increased risk of T2DM. In fact, there is much evidence that very low TG levels or very high HDL-C levels are associated with adverse effects on health and disease. Recently, Zhong et al. pooled 37 prospective cohort studies to conclude that HDL-C levels are associated with all-cause mortality, cardiovascular disease, and cancer in a J-shaped dose-response manner in the general population, implying that extremely high HDL-C levels are associated with an increased risk of death (20). Moreover, a Danish study found a U-shaped relationship between HDL-C concentration and all-cause mortality, in which mortality was higher in individuals with very high HDL-C levels (21). It has also been found that very high HDL-C levels do not represent a good prognosis, especially in young people (22). The mechanisms by which extremely high HDL-C levels are associated with an increased risk of death remain unclear. One possible explanation is that very high HDL-C levels may be due to genetic variants, leading to adverse health effects (23–25). Another explanation is that the conformation and function of lipoproteins in people with very high HDL-C levels may be impaired, resulting in the dysfunction of high-density lipoproteins, causing harm to the human body (26). Third, individuals with normal glycemic levels tend to ignore the risk of developing T2DM. The U-shaped relationship between TG/HDL-C ratio and the incidence of T2DM suggests that inappropriate TG/HDL-C ratio may be a potential intervention target to prevent the development of impaired glucose tolerance. Therefore, TG/HDL-C levels that are either too high or too low may be harmful.

4.2 Strengths and limitations of this study

Our study had several advantages over other studies: (1) our study was based on the NAGALA database, which has a complete and reliable clinical dataset. The sample size for assessing the association between TG/HDL-C ratio and the risk of incident T2DM was larger, the follow-up time was longer, and the TG/HDL-C ratio in our study had a more extensive range. These preconditions allowed us to assess the association more accurately between TG/HDL-C ratio and the risk of incident T2DM; (2) the populations were different. The data in our study were based on Japanese individuals, and we excluded those with prediabetes at baseline, i.e., those with HbA1c greater than 5.7%, and those with impaired fasting glucose levels. Therefore, our study is significant for the early detection and prevention of T2DM in Japanese men with normal blood glucose levels. (3) Our study adjusted for more confounding factors to make the conclusion more reliable and accurate.

Although our study has these advantages, it has many limitations. (1) The participants of our study were Japanese men. Therefore, our results should be interpreted cautiously due to sex and racial limitations. (2) We could not adjust for variables not included in the database itself, such as low-density lipoprotein cholesterol (LDL-C) and plasma insulin, because the original data were obtained from a public database. If possible, we will collect these data to further explore their relationship with T2DM risk. (3) We defined T2DM with baseline HbA1c and FPG levels, but without an oral glucose tolerance test (OGTT), so we may have underestimated the incidence of T2DM. (4) the pathogenesis and effect of TG/HDL-C on the risk of T2DM need to be further studied. (5) The AUC of ROC curves for TG, HDL-C, and TG/HDL-C were all lower than 0.7, indicating a poor prediction effect, which may be related to the small sample size. ROC curve evaluation is intended to provide research directions for subsequent researchers, and more studies are needed to obtain a more accurate prediction effect.

5 Conclusions

Our study is the first to show a U-shaped relationship between baseline TG/HDL-C ratio and new-onset T2DM in Japanese men with normal glucose levels. This result has a reference value for future mechanism and clinical research in related fields.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://datadryad.org/stash/dataset/doi:10.5061%2Fdryad.8q0p192.

Ethics statement

The studies involving humans were approved by Murakami Memorial Hospital Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

BS contributed to the design of the study and writing most of the first draft. KW and XZ organized the database and responded to the editor and reviewers. TY, WL, and TL performed the statistical analysis. GG and HF participated in the critical modification of important knowledge content. CL initiated the study design and ensured the accuracy or completeness of all questions in the study. All authors contributed to the article and approved the submitted version.

Funding

All costs of this study were supported by the National Natural Science Foundation of China (NSFC) Project 81974222.

Acknowledgments

We would like to thank the participants and the medical staff of the Medical Examination Center at Murakami Memorial Hospital. We also thank the members who participated in this cohort study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1180910/full#supplementary-material

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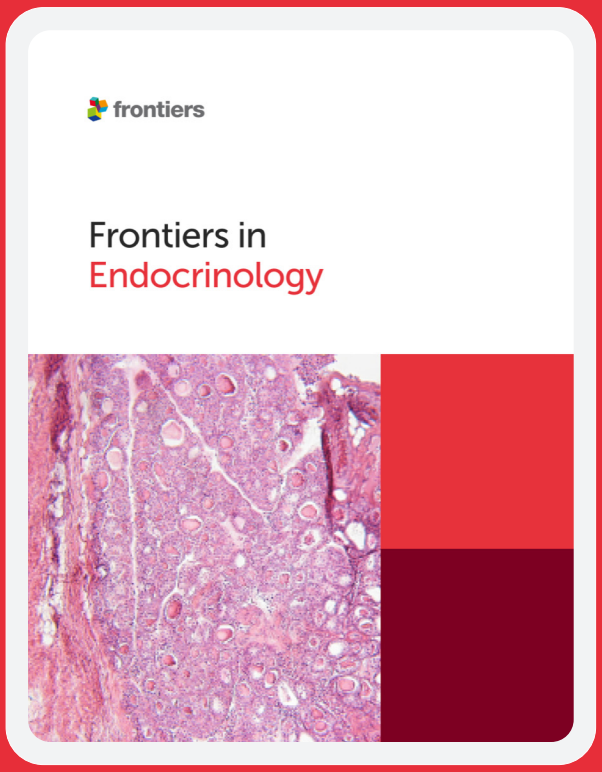

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