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New trends in type 2 diabetes diagnosis and management in primary care

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New trends in type 2 diabetes diagnosis and management in primary care

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Editorial: New trends in type 2 diabetes diagnosis and management in primary care

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type 2 diabetes, primary care, general practice, family medicine, multimorbidity, insulin resistance

Editorial on the Research Topic
New trends in type 2 diabetes diagnosis and management in primary care

Type 2 diabetes mellitus (T2DM) is a global health concern (1–3), with rising prevalence especially in middle and low income countries (4). In order to raise awareness and to timely diagnose this metabolic disorder, as well as to prevent further complications especially in poor countries, it is of paramount importance to enable cost effective and easy available approaches for the diagnosis and management of T2DM (5, 6). The following editorial aims to provide an overview of the latest trends related to T2DM diagnosis and management in a primary care setting.

Chen et al. proposed easily obtained and beneficial parameter, i.e. white blood cell (WBC) count for the early detection of insulin resistance (IR) as measured by Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index in the elderly Taiwanese and alerted primary care physicians to pay attention to this population group concerning the increased risk of IR. Similarly, Han et al. in a large national survey 2011-2016 conducted in the United States that encompassed more than 5,000 participants showed a positive correlation between another cost-effective biomarker, i.e. serum uric acid and the risk for IR. Chocair et al. suggested lower cut-offs for insulin (8 mU/L in men and 10 mU/L in women) and the HOMA-IR index (1.5 in men and 2.0 in women) in Brazilians and proposed new classification for metabolic syndrome (MetS), as following: metabolically normal: cut-off insulin level as mentioned above and without the International Diabetes Federation (IDF) criteria for MetS diagnosis; Level 1 MetS: hyperinsulinemia, in addition to one or two IDF criteria for MetS diagnosis; Level 2 MetS: hyperinsulinemia, in addition to three or more IDF criteria for MetS diagnosis.

Pi et al. explored the utility of point-of-care (POC) capillary glycated hemoglobin A1c (HbA1c) in primary healthcare settings given the fact that rural Chinese settings are limited for more expensive standardized HbA1c measurement method. They found a strong positive correlation between POC capillary and venous HbA1c values. Moreover, POC for HbA1c demonstrated high discriminatory ability for identification of patients with abnormal glucose regulation and undiagnosed diabetes.

Wang et al. proposed magnetic resonance spectroscopy (MRS) as an early imaging diagnostic and prognostic assessment of stroke. They applied MRS, in addition to clinical neurological deficit score (NIHSS) and HbA1c values in 53 T2DM patients within 24 h after the acute ischemic stroke (AIS) onset. A positive correlation between HbA1c values and NIHSS in T2DM patients with AIS was shown. The MRS and clinical NIHSS score showed high consistency in evaluating AIS.

In addition to timely manner diagnosis, prompt and multifactorial treatment and intervention could postpone the onset of T2DM-related complications.

Lin et al. compared the effects of metformin-based dual therapy vs. triple therapy on changes of glycemic and lipid parameters in 60 Taiwanese T2DM patients who were given at least 24 months of metformin monotherapy, dual therapy, i.e. with sodium-glucose cotransporter-2 (SGLT2) inhibitors or dipeptidyl peptidase 4 (DPP4) inhibitors or triple therapy with metformin plus linagliptin (DPP-4 inhibitor) and dapagliflozin (SGLT2 inhibitor). The authors found similar ability of glycemic control with dual therapy with metformin and linagliptin, just like with triple therapy. Although being effective, the mentioned triple therapy could be costly, so the authors recommended dual therapy with metformin and linagliptin as the better solution for long-term glycemic control due to similar glucose control ability of mentioned dual and triple therapy.

Vlacho et al. conducted a national cross-sectional study among physicians from a large number of Spanish primary care centers in an attempt to examine the degree of adherence with the therapeutic recommendations of the Clinical Practice Guidelines among recently diagnosed T2DM individuals, frail and obese subjects. They recorded adequate adherence for the majority of examinees with the highest percentage in the recently diagnosed T2DM individuals. On the other hand, Fu et al. conducted the study that included more than 10,000 patients with long-lasting T2DM with a median follow-up of 8.8 years and found significantly higher risk of all-cause mortality in T2DM patients that live alone as compared with those living with one or more adults, thus presuming that individuals who live alone exhibit an increasing tendency toward poor health behaviors.

Jie et al. identified factors related to the activities of daily living (ADL) limitations in China, i.e., a sedentary lifestyle, difficulty in sleeping and suffering from stroke or malignant tumor. They showed that those factors may increase the risk of ADL limitations among older (≥70 years) patients with T2DM, suggesting that identification of such factors may add reliable information to the development of targeted nursing practice and the improvement of health management for older T2DM patients.

Sukhram et al. recorded a significant relationship between serum cotinine (i.e., the key metabolite of nicotine and an indicator of cigarette smoke which is highly related to cardiovascular disease onset) and lipid parameters and their indexes in T2DM patients. The authors suggested the need for the modification of mentioned behavioral risk factor in an attempt to prevent comorbidities and advance cardiovascular health outcomes.

Zhao et al. described as moderately good typical behavioral characteristics of patients associated with integrated treatment and prevention (ITP) services for T2DM in China. The duration of disease, health insurance and treatment modality independently predicted the patients' behaviors associated with ITP services for T2DM. The authors pointed out the need for the development and implementation targeted interventions for different groups with the goal of improving T2DM patients' behaviors associated with ITP services.

In an attempt to evaluate the providers' T2DM care quality in rural China, Wu et al. applied standardized patients (SPs) method as the "gold standard" for examination of the quality of clinical practice. They recorded poor quality of T2DM care in rural regions of China, thus implying that the healthcare system in these areas is not capable to manage T2DM efficaciously and pointing out the need for the quest for potential interventions to improve the quality of the healthcare system in rural China.

Salinas Martínez et al. investigated realistic, idealistic and unrealistic expectations for drugs (metformin, glyburide and insulin) in primary care in T2DM patients since individuals with T2DM having positive outcome expectations are prone to benefit from T2DM management as compared with those with negative outcome expectations, whereas idealistic expectations are likely to exhibit the opposite effect on health outcomes. The authors have shown that personal preferences should be taken into account when medication adherence is concerned since almost half of the patients on insulin therapy would prefer to switch to oral antihyperglycemic agents as compared to 1/4 on metformin who would like the opposite. Sex, place of residence, time since diagnosis and diabetes education were the factors significantly correlated with the expectations in this study. The reinforcement of realistic expectations is needed.

This Research Topic sums up the current information and points out the new insights into the diagnosis of insulin resistance and management of diabetes in primary care. The up-to-date findings of studies that have been published in the current Research Topic proposed some cost effective and easy available diagnostics laboratory markers for insulin-resistance management and POC testing for glycated hemoglobin, in addition to some other more expensive procedures. Also, the need for raising awareness of this metabolic disease and the necessity for the modification of behavioral risk factors and potential interventions to ameliorate the quality of the healthcare system, especially in rural regions is of paramount importance. Additional studies are needed in the future focusing on raising awareness to beneficial health behaviors, as well to find the cost effective and easy available approaches for the diagnosis and therapeutic applications of T2DM.

Author contributions

AK and I-ST wrote the draft, reviewed, and revised the manuscript. All authors listed have made substantial, direct, and intellectual contributions to the work and approved it for publication.

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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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Significantly Increased Risk of All-Cause Mortality Among Type 2 Diabetes Patients Living Alone

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Background: There is a lack of studies evaluating the association between living status and subsequent outcomes in patients with type 2 diabetes (T2DM).

Objectives: This study aimed to assess the association between living alone and the risk of all-cause mortality in T2DM patients.

Methods: We performed a secondary analysis in patients with long-lasting T2DM from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study. The primary outcome was all-cause mortality. Multivariable Cox proportional hazard models was used to analyze and compare the hazard ratios (HRs) in patients living alone and with one or more adults.

Results: This study included 10,249 patients with T2DM. Of these, 2,078 (20.28%) were living alone and 8,171 (79.72%) lived with one or more adults. Over a median total follow-up of 8.8 years, 1,958 patients developed the primary endpoint. The all-cause mortality rates in patients living alone or living with one or more adults were 23.24 and 18.05%, respectively. Cox proportional hazard analysis showed that T2DM patients living alone had significantly higher rate of all-cause mortality than those living with others (HR, 1.34; 95% confidence interval [CI], 1.20–1.48; $p < 0.001$). After multivariable adjustment, living alone was an independent risk factor for all-cause mortality in patients with T2DM (adjusted HR, 1.27; 95% CI, 1.14–1.41; $p < 0.001$). Furthermore, the risks of both congestive heart failure (CHF) and fatal coronary heart disease (CHD) among 4,050 propensity score-matched patients were higher for patients living alone (respectively HR, 1.37; 95% CI, 1.08–1.74; $p = 0.010$; and HR, 1.16; 95% CI, 1.00–1.34; $p = 0.047$).

Conclusions: The risk of all-cause mortality was significantly higher in T2DM patients living alone than in those living with one or more adults.

Keywords: type 2 diabetes, living alone, all-cause mortality, hazard ratio, congestive heart failure (CHF), coronary heart disease (CAD)

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INTRODUCTION

The number of individuals living alone is increasing among older people in developing and developed countries, and this is considered an important demographic and social change (1). In 2017, 33.6% of the households in the European Union and around 40% of those in Nordic countries (except Iceland) consisted of one individual living alone (2). Complex reasons explain this trend, such as, for instance, trends

toward longevity, high divorce rates, high rates of widowhood, and low rates of intergenerational co-residence (3). Living alone may cause social isolation and feelings of loneliness and depression, especially when individuals perceive that their social needs are not met. The influence of social isolation on mortality and morbidity has been established among the traditional clinical risk factors (2, 4, 5). Meanwhile, loneliness and depression can negatively impact health and survival. Meta-analytic evidence demonstrates that loneliness is a predictor of all-cause mortality, showing that lonely people have a 22% higher risk of death than do non-lonely people (1). Moreover, living alone also entails a higher cost of living and may increase the economic burden of low-income people (6). Thus, living alone arises as a new concern with aging in patients with chronic non-communicable diseases.

Previous studies have demonstrated a significant association between living alone and mortality among older people (7, 8). The causal pathways connecting living alone with mortality are multifactorial. The social networks of individuals living alone tend to shrink, and these individuals are also likely to be in poorer health. Meanwhile, patients living alone have an increasing trend toward poor health behaviors (5, 9), and are also more likely to experience unmet care needs (10). In addition, several studies found that single living increased worse outcomes post heart attack or myocardial infarction (11, 12). More recently, our previous study demonstrated living alone is an independent risk factor for 1-year all-mortality in acute coronary syndrome patients ≥75 years of age (13). Given type 2 diabetes mellitus (T2DM) has been associated with the onset of atherosclerotic cardiovascular disease among older patients, often presenting as coronary heart disease (CHD), cerebrovascular disease, and cardiovascular death of atherosclerotic origin in patients (14), subsequently promoting premature aging. Therefore, there is an urgent need for cardiovascular events prevention in diabetic individuals. To achieve this goal, it is necessary to identify specific high-risk factors affecting the prognosis of T2DM in primary care.

The percentage of T2DM patients living alone has been reported to be ∼7–15% (15). To date, no study has prospectively assessed the association between living alone and incident T2DM, although cross-sectional studies have investigated living alone as a risk factor for T2DM (16, 17). As individuals with T2DM tend to live for a long time with advanced comorbidities, it is significant for public health to determine whether living status is independently associated with poor clinical outcomes. However, previous studies have exclusively focused on the relationship between living alone and the incidence of T2DM. Therefore, the present study examined the association between living alone and clinical outcomes in T2DM. We used the data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (18) and the ACCORD Follow-On Study (ACCORDION) (19) to assess the association between living arrangements and all-cause mortality in patients with T2DM.

METHODS

Study Participants and Data Collection

We performed a *post-hoc* analysis of the data from the ACCORD trial (ClinicalTrials.gov number, NCT00000620; data obtained from the Biologic Specimen and Data Repository Information Coordinating Center, National Heart, Lung and Blood Institute, U.S. Department of Health and Human Services). The rationale and design of the ACCORD trial have been described previously (20). Briefly, the ACCORD trial was a 2 × 2 factorial trial managed at 77 clinical sites in the United States and Canada, which recruited 10,251 T2DM patients aged between 40 and 79 years with glycosylated hemoglobin (HbA1c) concentration of 7.5% or more. The trial was designed to test whether the intensified control of blood glucose, blood pressure, and lipids could reduce the incidence of cardiovascular disease (CVD) in patients with T2DM. The included patients had a history of CVD, indicated by anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two risk factors for cardiovascular diseases. Intensive control of blood pressure and lipids did not reduce CVD. However, intensive glycemic intervention was discontinued after a mean follow-up of 3.7 years because of the increased mortality in the intensive glycemic control group, and all participants were transitioned to standard glycemic control intervention. The ACCORD closeout visits were completed in June of 2009. Follow-up continued for the remaining participants in the ACCORDION trial, with a total follow-up period of 8.8 years. Ethics approval and consent to participate were not applicable.

Exposure Variables

We excluded participants whose living arrangement baseline data were missing ($n = 2$). This resulted in a final sample of 10,249 participants for the analysis of the association between baseline living status and clinical outcomes. Living arrangement status at baseline was documented as either living alone or living with one or more adults. Further information collected at baseline included demographics, medical history, previous cardiovascular events, mental health, laboratory values (e.g., fasting blood glucose, HbA1c, estimated glomerular filtration rate (eGFR), total cholesterol, and triglycerides), and current chronic drug regimen.

Study Outcomes and Definitions

The primary outcome of this study was all-cause mortality. Secondary endpoints were cardiovascular mortality, non-fatal stroke, non-fatal myocardial infarction (MI), congestive heart failure (CHF), and fatal coronary heart disease (CHD). Patients were followed up every 2–4 months through phone interviews or visits at the outpatient clinic. At 4-month intervals, the relevant medical information was collected. The study outcomes were classified by the Working Group of the Morbidity and Mortality subcommittee.

Statistical Analysis

Qualitative demographic data are presented as numbers (percentages), and baseline characteristics of patients living alone and living with others were compared using the chi-square test. Quantitative data are presented as mean ± SD, and the Student's *t*-test was used to compare baseline characteristics. Kaplan-Meier survival curves were used to analyze primary and secondary outcomes in patients living alone or living

with others, and the differences between groups in cumulative incidence curves were compared using the log-rank test. A Cox proportional hazards regression model was used to calculate the hazard ratio (HR) and 95% confidence intervals (CIs) for the primary and secondary outcomes in the comparisons of patients living alone or living with others. The proportional hazards assumption was examined using Schoenfeld residuals. Three multivariable models with progressive degrees of adjustment were used to adjust for potential confounders of the study outcomes. Model 1 was adjusted for age, sex, race, body mass index (BMI), previous cardiovascular events, education level, systolic blood pressure (SBP), diastolic blood pressure (DBP), and smoking status. Model 2 was further adjusted for other clinical variables, including duration of diabetes, eGFR, HbA1c, total plasma cholesterol, plasma high-density lipoprotein cholesterol (HDL-C), plasma low-density lipoprotein cholesterol (LDL-C), and depression status. Model 3 was further adjusted for the use of statins, biguanide, aspirin, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), and insulin.

The primary and secondary outcomes in propensity score-matched patients with different living statuses were determined using Cox proportional hazard analysis. We used 1:1 nearest-neighbor matching without replacement to match all the baseline characteristics. The propensity score was calculated using a logistic regression model. Standardized differences <0.10 between propensity score-matched patients were considered negligible. The effect of living alone in patients with T2DM was further analyzed according to subgroup analysis: sex (male or female), age (<60 or ≥60 years), race (white or non-white), CVD (CVD history or no CVD history), HbAc1 level (<8.0% or ≥8.0%), depression (depression or non-depression), smoking (no history of smoking or history of smoking), and use of insulin or statins. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using the Statistical Product and Service Solution version 25 (IBM, Armonk, NY, USA).

RESULTS

Baseline Characteristics According to Living Arrangement

A total of 10,249 patients were eligible for inclusion in this analysis, including 2,078 documented as living alone (20.28%) and 8,171 (79.72%) living with one or more adults. Patients enrolled in the current study were 62.76 ± 6.64 years old on average. The baseline characteristics are shown in **Table 1.** Participants living alone were older and more often female and white. They had higher BMI, heart rate (HR), HbAc1, total cholesterol, LDL-C, urinary creatinine, urinary albumin, and lower levels of eGFR than those living with one or more adults (all $P < 0.001$). Likewise, participants living alone had more frequent smoking history, higher prevalence of CVD, prior hospitalization for heart failure (HF), depression, and CHF, were more prone to taking metformin and insulin, and less prone to take statins than patients living with one or more adults (all $P < 0.001$).

Association Between Living Arrangement and All-Cause Mortality

During a median follow-up of 8.8 years, 1,958 patients (19.10%) developed all-cause mortality. As **Table 2** shows, the incidence of all-cause mortality was higher in patients who lived alone than in those living with other adults (483 [23.24%] vs. 1,475 [18.05%], $P = 0.001$). In the unadjusted model, patients living alone had a higher risk of all-cause mortality (HR, 1.34; 95% CI, 1.20-1.48; $P < 0.001$) and non-fatal stroke (HR, 1.26; 95% CI, 1.02-1.56; $P = 0.030$) than those living with one or more adults. There was no difference in the rates of cardiovascular mortality, non-fatal MI, CHF, or CHD. Kaplan-Meier survival curves and cumulative event rates for the primary and secondary outcomes in patients with different living statuses are shown in **Figure 1** and **Table 2**, respectively. In the multivariable model, there remained statistically significant differences in all-cause mortality (model 1: adjusted HR, 1.31; 95% CI, 1.18–1.46; $P < 0.001$; model 2: adjusted HR, 1.27; 95% CI, 1.14–1.41; $P < 0.001$; model 3: adjusted HR, 1.27; 95% CI, 1.14–1.41; $P < 0.001$). There were no differences between patients living alone and those living with one or more adults in cardiovascular mortality, non-fatal MI, non-fatal stroke, CHF, and CHD.

We used propensity score matching as a sensitivity analysis to verify the association between living alone and the risk of primary and secondary outcomes in patients with T2DM. Among the propensity score-matched patients (n=4,050), the risk of all-cause mortality (HR, 1.34; 95% CI, 1.17–1.53; $P < 0.001$), CHF (HR, 1.37; 95% CI, 1.08–1.74; $P = 0.010$), and CHD (HR, 1.16; 95% CI, 1.00–1.34; $P = 0.047$) were significantly higher in patients living alone than in those living with one or more adults, whereas there were no differences in the risk of adverse CV events, cardiovascular mortality, non-fatal stroke, and non-fatal MI. Kaplan-Meier survival curves and cumulative event rates for primary and secondary outcomes are shown in **Figure 2**.

Association Between Living Arrangements and All-Cause Mortality in Different Subgroups

Interaction and stratified analyses were performed to evaluate the association between living arrangements and all-cause mortality in the different subgroups (**Figure 3**). We did not find interactions among age, sex, previous history of CVD, depression status, smoking history, HbA1C, use of insulin, or use of statins, suggesting that the results of different subgroups are consistent and reliable.

DISCUSSION

In this study, we found an association between living alone and mortality in T2DM. Unadjusted analysis showed that people living alone had a higher incidence of all-cause mortality (the primary endpoint) and non-fatal stroke. However, there were no differences in CV mortality, non-fatal MI, CHF, or CHD between the two groups. Importantly, living alone in patients with T2DM was independently associated with an increased risk of all-cause mortality after adjusting for confounding variables.

TABLE 1 | Characteristics of patients with different living status.

Variable	All (n = 10,249)	Living alone		P-value
		No (n = 8,171)	Yes (n = 2,078)	
Age (year; mean ± SD)	62.76 ± 6.64	62.54 ± 6.58	63.66 ± 6.79	<0.001
Sex no. (%)				
Male	6,299 (61.46%)	5,323 (65.15%)	976(46.97%)	<0.001
Female	3,950 (38.54%)	2,848 (34.85%)	1,102 (53.03%)	
Race no. (%)				<0.001
White	6,392 (62.37%)	5,177 (63.35%)	1,215 (58.47%)	
Non-white	3,857 (37.63%)	2,994 (36.64%)	863 (41.53%)	
Median duration of diabetes (year; mean ± SD)	10.80 ± 7.60	10.77 ± 7.52	10.93 ± 7.89	0.407
Median duration of hyperlipidemia (year; mean ± SD)	5.96 ± 5.70	5.95 ± 5.66	5.96 ± 5.86	0.985
Median duration of hypertension (year; mean ± SD)	10.23 ± 9.58	10.12 ± 9.45	10.67 ± 10.09	0.049
Previous cardiovascular events no. (%)	3,608 (35.20%)	2,942 (36.01%)	666 (32.05%)	0.001
Smoking status no. (%)				0.387
No smoking	4,294 (41.09%)	3,406 (41.68%)	888 (42.73%)	
Smoking	5,955 (58.0%)	4,765 (58.32%)	1,190 (57.27%)	
Education no. (%)				
Less than high school graduate	1,521 (14.84%)	1,219 (14.92%)	302 (14.53%)	0.665
High school graduate	2,704 (26.38%)	2,169 (26.55%)	535 (25.75%)	0.467
Some college or technical school	3,357 (32.75%)	2,653 (32.47%)	704 (33.88%)	0.216
College degree or higher	2,661 (25.96%)	2,126 (26.02%)	535 (25.75%)	0.809
Previous heart failure no. (%)	494 (4.82%)	386 (4.72%)	108 (5.02%)	0.369
Depression no. (%)	2,419 (23.60%)	1,797 (21.99%)	622 (25.71%)	0.000
Heart rate (mean ± SD)	72.65 ± 11.82	72.34 ± 11.64	73.88 ± 12.43	<0.001
SBP (mmHg, mean ± SD)	136.36 ± 17.11	136.31 ± 16.97	136.56 ± 17.66	0.564
DBP (mmHg, mean ± SD)	74.89 ± 10.58	74.89 ± 10.58	74.83 ± 10.96	0.822
BMI (mean ± SD)	32.22 ± 5.42	30.10 ± 5.38	32.68 ± 5.57	<0.001
Glycated hemoglobin (%, mean ± SD)	8.30 ± 1.06	8.2 ± 1.05	8.4 ± 1.07	0.011
eGFR (mL/min, mean ± SD)	91.05 ± 27.15	91.48 ± 27.50	89.36 ± 56.70	0.001
FPG (mg/dL, mean ± SD)	175.19 ± 56.18	174.7 ± 55.79	177.12 ± 57.66	0.087
ALT (U/L, mean ± SD)	27.58 ± 16.19	27.97 ± 16.68	26.05 ± 13.98	<0.001
Potassium (mg/dL, mean ± SD)	4.48 ± 0.47	4.48 ± 0.47	4.46 ± 0.49	0.194
Cholesterol (mg/dL, mean ± SD)	183.29 ± 41.85	182.45 ± 41.69	186.56 ± 42.50	0.001
Triglyceride (mg/dL, mean ± SD)	190.13 ± 148.40	190.5 ± 143.81	188.26 ± 165.30	0.559
Low-density lipoprotein (mg/dL, mean ± SD)	104.89 ± 33.93	104.37 ± 33.67	106.97 ± 34.79	0.002
High-density lipoprotein (mg/dL, mean ± SD)	41.86 ± 11.62	41.41 ± 11.25	43.63 ± 12.79	<0.001
Serum creatinine (mg/dL, mean ± SD)	0.91 ± 0.23	0.91 ± 0.23	0.91 ± 0.24	0.883
Urinary albumin (mg/dL, mean ± SD)	10.27 ± 36.60	9.77 ± 34.75	12.23 ± 42.08	0.017
Urinary creatinine (mg/dL, mean ± SD)	124.41 ± 66.25	123.10 ± 65.16	129.54 ± 70.14	<0.001
Medications no. (%)				
Insulin	3,581 (34.94%)	2,816 (34.46%)	765 (36.81%)	0.045
Metformin	6,553 (63.94%)	5,277 (64.58%)	1,276 (61.41%)	0.007
ACEI/ARB	7,100 (69.28%)	5,662 (69.29%)	1,438 (69.20%)	0.935
Statin	6,499 (63.41%)	5,238 (64.10%)	1,261 (60.68%)	0.004
Aspirin	5,579 (54.43%)	4,456 (54.53%)	1,123 (54.04%)	0.688
MMSE score (mean ± SD)	27.40 ± 2.51	27.39 ± 2.52	27.44 ± 2.47	0.634
All-cause mortality	1,958 (19.10%)	1,475 (18.05%)	483 (23.24%)	<0.001

Values are mean ± SD or %. DBP, diastolic blood pressure; SBP, systolic blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; ALT, Alanine aminotransferase; MMSE, mini-mental State Examination; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction.

TABLE 2 | The risk of primary and second outcomes in T2DM Patients with different living status.

Characteristics	Living with others	Living alone	*p*-value
All-cause mortality			
Cases/*n*	1,475/8,171	483/2,078	
Unadjusted HR (95% CI)	1.00 (ref)	1.34 (1.20–1.48)	<0.001
Model 1: adjusted HR (95% CI)	1.00 (ref)	1.31 (1.18–1.46)	<0.001
Model 2: adjusted HR (95% CI)	1.00 (ref)	1.27 (1.14–1.41)	<0.001
Model 3: adjusted HR (95% CI)	1.00 (ref)	1.27 (1.14–1.41)	<0.001
Cardiovascular mortality			
Cases/*n*	535/8,171	134/2,078	
Unadjusted HR (95% CI)	1.00 (ref)	1.02 (0.84–1.23)	0.858
Model 1: adjusted HR (95% CI)	1.00 (ref)	1.03 (0.85–1.25)	0.782
Model 2: adjusted HR (95% CI)	1.00 (ref)	1.02 (0.83–1.24)	0.871
Model 3: adjusted HR (95% CI)	1.00 (ref)	1.02 (0.83–1.24)	0.881
Non-fatal MI			
Cases/n	738/8,171	198/2,078	
Unadjusted HR (95% CI)	1.00 (ref)	1.09 (0.94–1.28)	0.261
Model 1: adjusted HR (95% CI)	1.00 (ref)	1.13 (0.96–1.33)	0.130
Model 2: adjusted HR (95% CI)	1.00 (ref)	1.08 (0.92–1.27)	0.359
Model 3: adjusted HR (95% CI)	1.00 (ref)	1.08 (0.92–1.27)	0.349
Non-fatal stroke			
Cases/n	374/8,171	114/2,078	
Unadjusted HR (95% CI)	1.00 (ref)	1.26 (1.02–1.56)	0.030
Model 1: adjusted HR (95% CI)	1.00 (ref)	1.25 (1.01–1.55)	0.042
Model 2: adjusted HR (95% CI)	1.00 (ref)	1.18 (0.94–1.46)	0.149
Model 3: adjusted HR (95% CI)	1.00 (ref)	1.18 (0.95–1.47)	0.145
CHF			
Cases/n	549/8,171	147/2,078	
Unadjusted HR (95% CI)	1.00 (ref)	1.14 (0.95–1.36)	0.168
Model 1: adjusted HR (95% CI)	1.00 (ref)	1.10 (0.91–1.33)	0.306
Model 2: adjusted HR (95% CI)	1.00 (ref)	1.08 (0.89–1.30)	0.446
Model 3: adjusted HR (95% CI)	1.00 (ref)	1.07 (0.89–1.30)	0.468
CHD			
Cases/*n*	1,471/8,171	388/2,078	
Unadjusted HR (95% CI)	1.00 (ref)	1.08 (0.97–1.21)	0.157
Model 1: adjusted HR (95% CI)	1.00 (ref)	1.14 (1.01–1.28)	0.027
Model 2: adjusted HR (95% CI)	1.00 (ref)	1.11 (0.98–1.24)	0.091
Model 3: adjusted HR (95% CI)	1.00 (ref)	1.11 (0.99–1.24)	0.082

Model 1, the following parameters were adjusted: age, sex, previous cardiovascular events, race, BMI, education, SBP, DBP, and smoking status.
Model 2, the following parameters were adjusted: age, sex, previous cardiovascular events, race, education, duration of diabetes, SBP, DBP, smoking status, eGFR, HbA1c, total plasma cholesterol, plasma HDL-C, plasma LDL-C, and depression.
Model 3, the following parameters were adjusted: age, sex, previous cardiovascular events, race, BMI, education, duration of diabetes, depression, SBP, DBP, smoking status, eGFR, HbA1c, total plasma cholesterol, plasma HDL-C, plasma LDL-C, use of statin or biguanide, aspirin, ACEI/ARB, and insulin.

However, the adjusted analysis revealed that living alone was not an independent predictor of non-fatal stroke. These results highlight the clinical importance of living status in individuals with T2DM. The association between living alone and increased risk of all-cause mortality was observed among the prespecified subgroups. This phenomenon could be significant for public health in consideration of the increasing incidence of living alone and how society as a whole and its healthcare systems adapt to this transformation.

The incidence of living alone continues to grow in the general population, and the present study showed that 20.28% of the ACCORD participants were living alone. Living status has been suggested as a risk factor for T2DM. T2DM patients are diverse in terms of ethnicity, life behaviors, socioeconomic status, and psychosocial factors that may play a role in the prognosis of T2DM. Previous studies revealed that the association between living alone and mortality persisted significantly, even after controlling for confounding variables (21). However, few studies have investigated the relationship between living alone and prognosis in patients with T2DM. Hence, it is necessary to evaluate the relationship between living status and adverse events in T2DM patients.

The present study demonstrated that T2DM patients living alone were characterized by older age, higher prevalence of cardiovascular events, higher prevalence of smoking habits, higher BMI, and higher levels of total cholesterol and LDL-C than those living with others. These findings suggest that multifactorial lifestyle modification interventions are likely to be effective in improving the prognosis of T2DM patients living alone. Moreover, our results showed that patients living alone had lower quality of life, suggesting a critical need for adjusting treatment and management strategies to improve the quality of life of these patients.

Our results expanded previous understanding and confirmed that living alone is an independent risk factor for the prognosis of T2DM patients in a long-term follow-up. However, the potential mechanisms underlying such association are unclear, several factors have been found to be associated with mortality. Several studies have found that individuals living alone have worse self-perceived health and quality of life, depression, and feelings of loneliness (22–24). Consistent with previous reports, our study further confirmed that T2DM patients living alone experienced more feelings of depression (25.71% vs. 21.99%, $P < 0.001$). Moreover, numerous studies have shown that depression is associated with a higher mortality rate (25). Katon et al. conducted a study on 4,000 patients with T2DM. Over a 3-year follow-up, the mortality in patients with mild or severe depression was 1.7 and 2.3 times higher, respectively, than that of patients without depression (26). Similar findings were reported by Zhang et al. in a survival analysis using the National Health and Nutrition Examination Survey (NHANES)-I data (27).

The majority of studies have also found that living alone is associated with poor diabetes self-care, and especially poor dietary arrangements (28). Dietary patterns are closely related to the optimal management of T2DM in the general population (28–30). The diverse features of people living alone and complex social and demographic changes could influence the dietary patterns of patients with T2DM. All these factors could affect compliance with the guidelines to optimize nutritional status. The relationship between living alone and dietary patterns has also been discussed previously (31, 32). Although a few studies found some healthy behaviors in patients living alone, most studies found that a larger number of patients living alone are

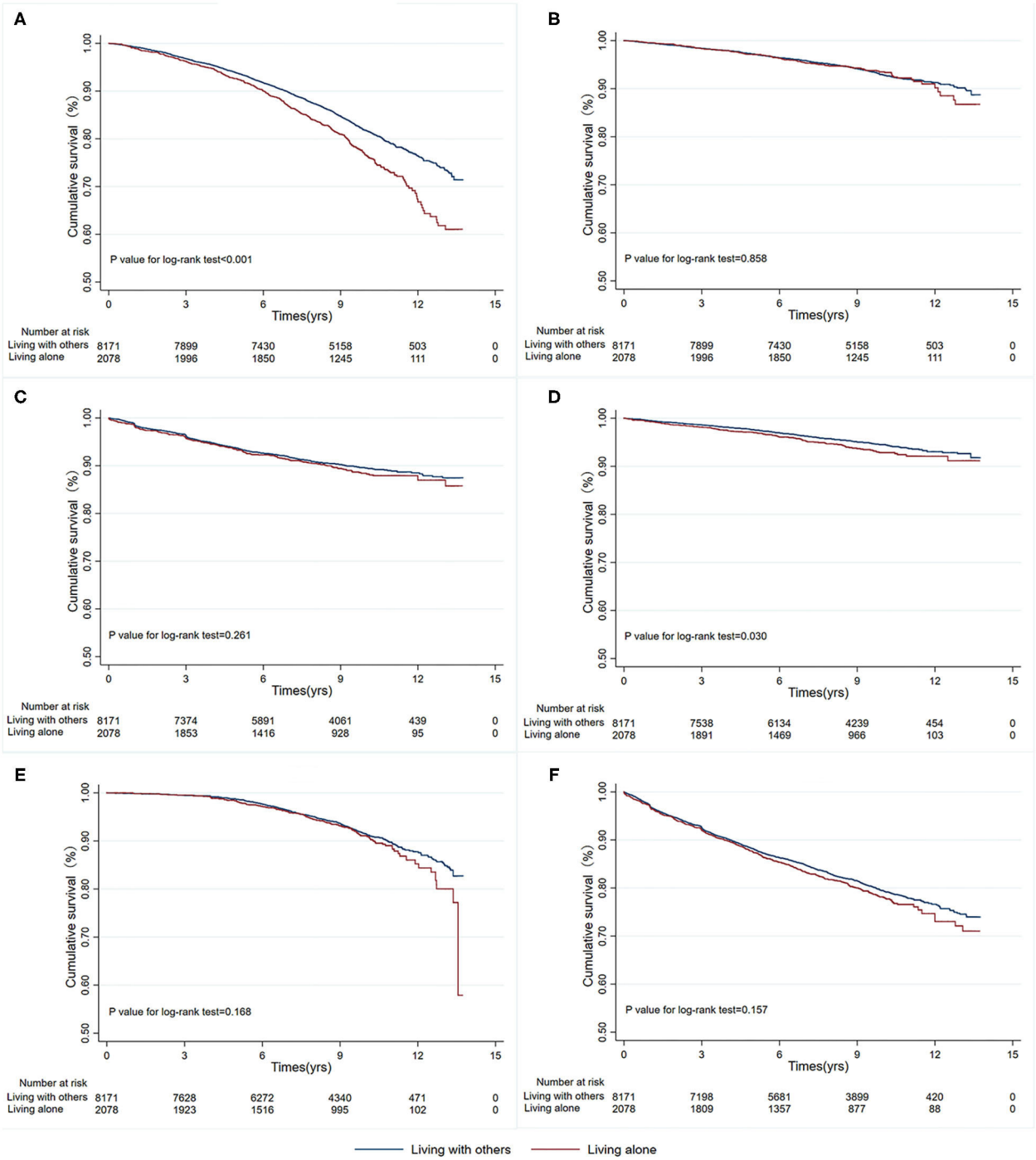

FIGURE 1 | Kaplan-Meier survival curves for primary and secondary outcomes by living status. **(A)** All-cause mortality; **(B)** Cardiovascular mortality; **(C)** Non-fatal MI; **(D)** Non-fatal stroke; **(E)** CHF; **(F)** CHD. MI, myocardial infarction; CHF, congestive heart failure; CHD, coronary artery disease.

less likely to follow healthy dietary habits, including the intake of diverse foods and the consumption of fruits and vegetables (31, 33). Furthermore, there is a possibility that a decline in motivation and pleasure in cooking and/or eating in people living alone, which often manifests in the cooking of simple meals or the consumption of ready-made food. The likely consequences are difficulty in following healthy eating recommendations and in controlling portion size. Aspects of psychological and mental

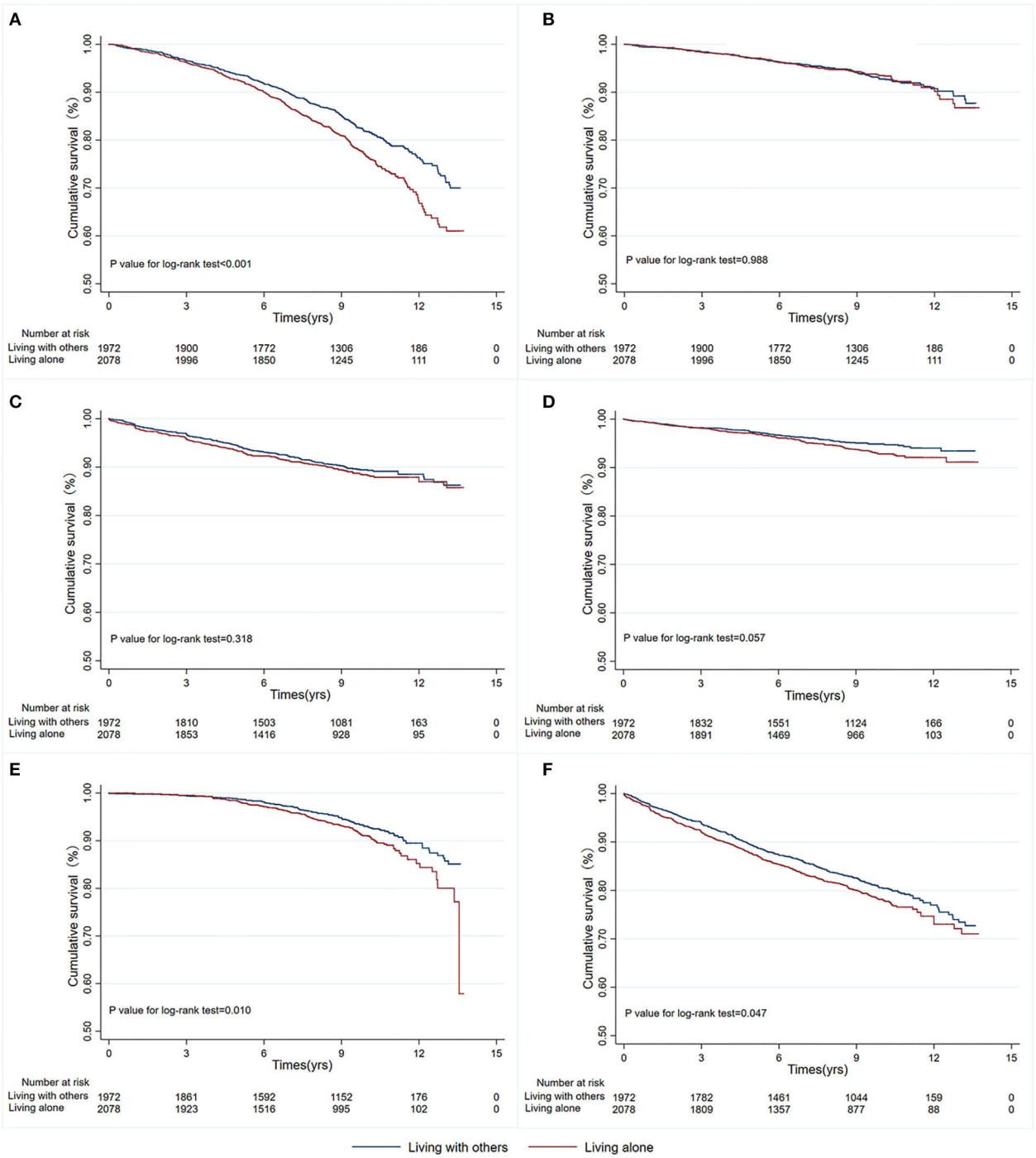

FIGURE 2 | Kaplan-Meier survival curves for primary and secondary outcomes in propensity score-matched patients with different living status. **(A)** All-cause mortality; **(B)** Cardiovascular mortality; **(C)** Non-fatal MI; **(D)** Non-fatal stroke; **(E)** CHF; **(F)** CHD. MI, myocardial infarction; CHF, congestive heart failure; CHD, coronary artery disease.

health related to living alone could also affect food intake, resulting in increased or decreased dietary intake.

Previous studies have found that T2DM patients living alone show poor medication adherence, including to prescribed medications and blood measurements. Strict glycemic management is associated with a decreased risk of diabetes-related complications, especially in individuals who have not suffered years of uncontrolled HbA1c levels (34). Projections

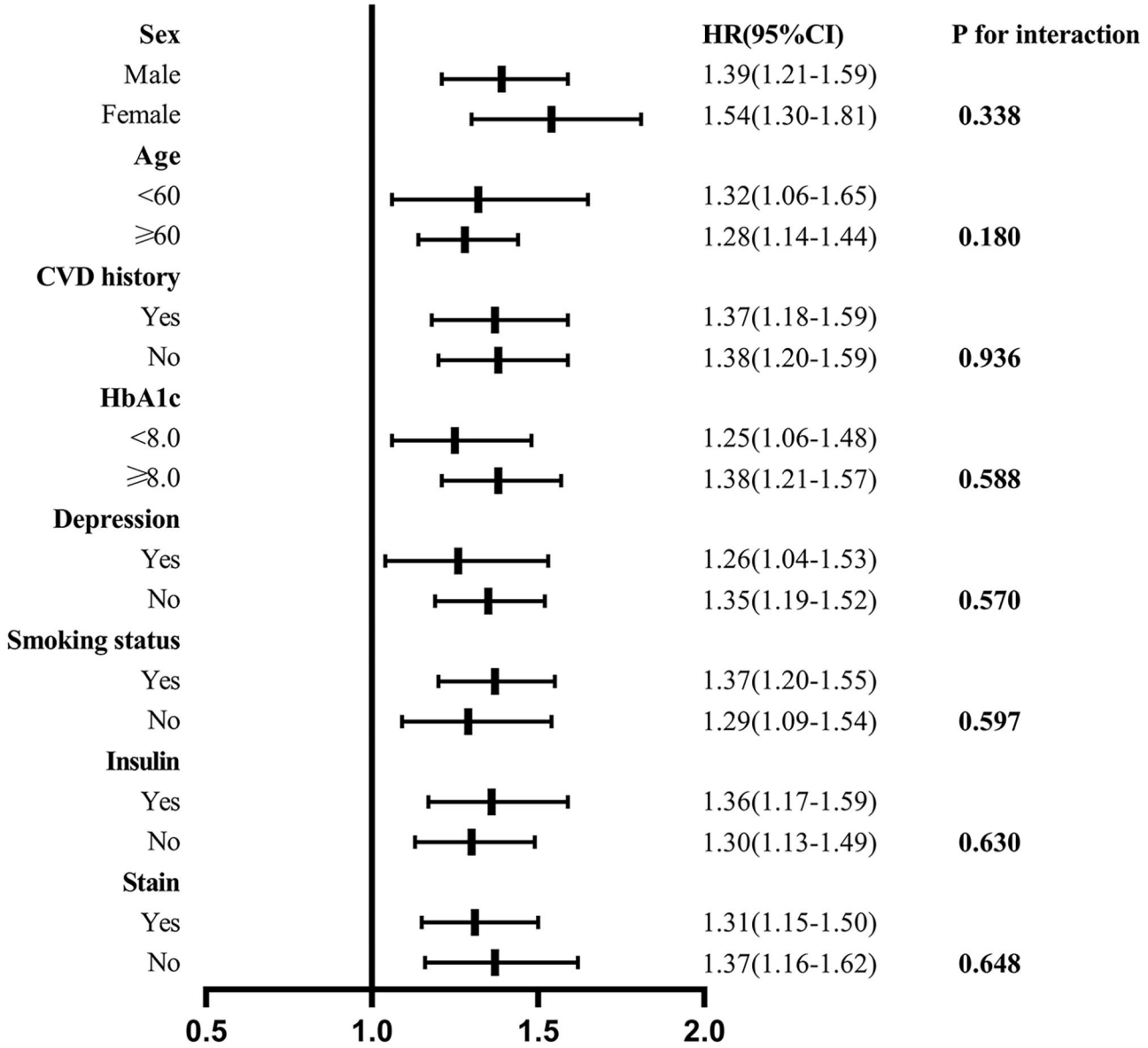

FIGURE 3 | Association between living alone and all-cause mortality in the subgroups. Interaction and stratified analyses were performed to evaluate the association between living arrangements and all-cause mortality in the different subgroups.

from the observational United Kingdom Prospective Diabetes Research (UKPDS 35) proposed that a 1 percent decrease in mean HbA1c would lead to a 14% lower risk of all-cause mortality, 21% lower rate of diabetes-related mortality, and 37% decline in the risk of microvascular complications (35). Spencer et al. suggested that education and support from peers allow T2DM patients to achieve better self-management in the long term, leading to good efficacy of HbA1c control (36). A link between living alone and worse HbA1c management has also been observed in a recent study (37). Our results are consistent with those previous findings, as the mean HbA1c level in T2DM patients living alone in our study was higher than that in patients living with one or more adults.

We also found that the risk of CHF and CHD was significantly higher in individuals living alone among propensity score-matched patients. Recent research has described the association between living alone and the incidence of adverse cardiovascular events (35, 38). The Coronary Revascularization Demonstrating Outcome Study in Kyoto of Acute Myocardial Infarction Registry (CREDO—Kyoto AMI) showed that, in a 5-year follow-up, individuals living alone had higher risk of admission for HF (39). The Reduction of Atherothrombosis for Continued Health (REACH) study also showed that living alone was associated with a higher risk of mortality and CV death (40). A possible explanation is that living alone may increase anxiety and depression, causing more psychological distress,

poor handling mechanisms and self-care, less access to healthcare services, and less insistence on guideline-recommended therapy and secondary prevention targets.

LIMITATIONS

The first limitation of this study is that it was a *post-hoc*, exploratory analysis of the ACCORD data; randomization may break, and residual and uncontrolled confounding may still be present. Additionally, the data included in the present study, derived from clinical trials, may not be representative of real-world populations of patients with T2DM. Third, we were unable to account or adjust for unidentified confounders, such as stress and socioeconomic status. Unfortunately, although the statistical modeling included multiple factors, including psychosocial factors and medical history, we acknowledge that there remains a potential for residual confounding. Fourth, living alone was assessed only once at baseline: we did not re-evaluate the living status during follow-up, during which cohabitation status or social circumstances may have changed. Information from prospective clinical trials is needed to clarify the practical effects of living alone in patients with T2DM.

CONCLUSION

The present study suggests that living status may be a strong marker for predicting the prognosis of T2DM patients, an observation which warrants confirmation in further studies. The main significance of the present study was the identification of specific high-risk factors affecting the prognosis of T2DM. Therefore, these findings have potential implications for public health. Society as a whole needs to be prepared to the negative effects of the increasing rate of individuals living alone.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. The datasets are available from the ACCORD/ACCORDIN Research Materials obtained from the National Heart, Lung, and Blood Institute (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Second Xiangya Hospital of Central South University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

This study was completed in collaboration with the following authors: YW and ST defined the study theme and methods. LF, YZ, and JS analyzed the data. LF wrote the paper. ZX and ST edited the paper. All authors have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.782751/full#supplementary-material

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The Association Between White Blood Cell Count and Insulin Resistance in Community-Dwelling Middle-Aged and Older Populations in Taiwan: A Community-Based Cross-Sectional Study

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Background: Insulin resistance (IR) is a major pathophysiological factor in the development and progression of diabetes mellitus (DM). DM is highly prevalent in Taiwan and has become one of the most common health problems in family medicine and primary care. We aimed to use white blood cell count (WBC), a common physiological parameter, to develop a simple clinical prediction rule for IR in the middle-aged and old Taiwanese population.

Methods: In this cross-sectional community-based study, the participants completed a questionnaire comprising personal and medical history data and underwent anthropometric measurements and blood sampling. IR was defined as a HOMA-IR index $\geq$2. Independent *t*-test, Mann–Whitney U test, chi-square test, Pearson's correlation test, multivariate binary logistic regression, and receiver operating characteristic curves were used to evaluate the association between the WBC count and IR.

Results: A total of 398 community-dwelling middle-aged and older persons (34.9% men) with a mean age of 64.43 $\pm$ 8.45 years were enrolled for the analysis. A significant association was identified between the WBC counts and IR, with a Pearson's correlation coefficient of 0.37 (p-value $<$ 0.001). Multivariate logistic regression revealed that WBC count (OR = 1.50; 95% CI = 1.25–1.81) was an independent risk factor for IR after adjusting for confounding variables. The area under the receiver operating characteristic curve for WBC count was 0.67, and the optimal threshold value was 5.65 1,000/uL.

Conclusion: A high WBC count is positively related to an increased risk of IR among middle-aged and older people in Taiwan.

Keywords: insulin resistance, anthropometry, cardio-metabolic risk factors, prediction, white blood cell count

INTRODUCTION

Insulin resistance (IR) is recognized as a serious public health problem worldwide and has emerged as a major pathophysiological factor in the development and progression of type 2 diabetes mellitus (T2DM) and metabolic disease (1–4). The hyperinsulinemic euglycemic clamp test, the gold standard for assessing IR, has been used to quantify IR using a variety of methods. However, this test is expensive, invasive, and time-consuming, making it unsuitable for clinical purposes or large-scale studies (5). Therefore, the homeostasis model assessment of IR (HOMA-IR) is used to evaluate IR (6, 7).

According to a national study, the prevalence of T2DM between 2017 and 2020 was 11.05% in Taiwan (8). As IR is a risk factor for the development of T2DM, the early identification of IR is important from a public health perspective. Currently, there are few standard methods for quantifying IR. The lack of standardized insulin assays has limited the clinical utility of HOMA-IR, although it has been widely used in the study of metabolic syndrome (9). Although HOMA-IR is used for quantifying IR, it is not routinely conducted in clinical practice. Therefore, a simple and more accessible marker for predicting IR may be useful for the early identification of individuals with IR. In clinical practice, evaluating IR using the HOMA-IR index is often difficult as insulin and fasting glucose levels are not routinely measured.

Growing evidence indicates that IR is closely associated with chronic subclinical inflammation (10–12). Biomarkers associated with inflammation, such as white blood cell (WBC), C-reactive protein and interleukin-6 levels, are considered as independent predictors of cardiovascular disease and T2DM in adults, (13–15). Among these biomarkers, the WBC count is commonly measured and is more cost-effective. However, few studies have examined the association between WBC count and IR measured by HOMA-IR. Some studies have proposed that the circulating WBC count is a biomarker for the prognoses of cardiovascular risk and IR (16–18), but the possibility of identifying IR using elevated WBC counts has not been fully investigated.

The major purpose of this study was to establish a simple clinical marker for the early identification of IR in the middle-aged and older populations in Taiwan. Additionally, our study results may provide valuable information for primary care physicians to alert subjects in this age group regarding the increased risk of IR.

Abbreviations: HOMA-IR, Homeostasis model assessment of insulin resistance; IR, Insulin resistance; T2DM, Type 2 Diabetes mellitus; WBC, White blood cell count; CRP, C-reactive protein; BMI, Body Mass Index; WC, Waist Circumference; BP, Blood pressures; FPG, Fasting plasma glucose; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; TG, Triglyceride; ROC, Receiver operating characteristic; AUC, Area under the ROC curve; HTN, Hypertension; aOR, Adjusted odds ratio; IDF, International Diabetes Federation.

MATERIALS AND METHODS

Study Design and Participants

This was a cross-sectional, community-based study conducted between January and October 2014. Data for this study were collected from a community health promotion project of the Linkou Chang Gung Memorial Hospital. We recruited 619 volunteers aged ≥50 years from eight cluster-randomized of 28 villages in Guishan district, Taoyuan city. The inclusion criteria were as follows: (1) subjects aged 50 years or above and (2) subjects residing in Guishan district for at least half a year. The exclusion criteria were as follows: (1) subjects with functional disability, (2) subjects who declined to participate, (3) subjects who could not complete all the examinations or face-to-face interviews, and (4) subjects with outliers of HOMA-IR level. A total of 398 participants, including 139 men and 259 women, were included in the analysis. Each participant completed a questionnaire that included personal information and medical history through face-to-face interviews conducted by trained research assistants. The project was approved by the Institutional Review Board of Linkou Chang Gung Memorial Hospital (102-2304B), and all the participants were fully informed and signed informed consent forms before enrollment.

Anthropometric and Laboratory Examinations

After obtaining informed consent, detailed anthropometric measurements (such as height, weight, age, and waist circumference [WC], and blood sampling were conducted by trained research nurses under the supervision of a medical doctor. Height was measured using calibrated height meters while the participant stood erect and barefooted, with feet placed together and facing forward. Body mass index (BMI) was calculated as weight divided by the square of the height (kg/m^2). The WC was measured at the level midway between the iliac crest and the lower border of the 12th rib while the participant stood with feet 25–30 cm apart. Blood pressure was measured using an automated sphygmomanometer after a 10-mins rest in a seated position, and the lowest reading was recorded. WBC count and clinical biochemistry tests were performed in a hospital laboratory accredited by the College of American Pathologists; and, these included fasting plasma glucose (FPG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol, triglyceride (TG), and serum creatinine levels. Venous blood samples were collected after overnight fasting for at least 12 h. A standardized biochemistry analyzer (Hitachi LST008, Hitachinakashi, Japan) was used for the determination of laboratory tests. A standardized Sysmex XN series analyzer (Sysmex XN 9000) was used for the determination of WBC.

Definitions of Hypertension, Diabetes Mellitus, and Hyperlipidemia

Hypertension (HTN) was defined by a systolic blood pressure (SBP) ≥ 140 mmHg or a diastolic blood pressure (DBP) ≥ 90 mmHg, the current use of antihypertensive medications, or

TABLE 1 | General characteristics of the study population according to IR group and non-IR group.

Variables	Total	Insulin Resistance		
		IR group (≥2)	Non-IR group (<2)	p value
	(n = 398)	(n = 123)	(n = 275)	
Age (year)	64.43 ± 8.45	63 [59, 71]	63 [58, 70]	0.68
SBP (mmHg)	129.57 ± 16.72	133.97 ± 16.49	127.60 ± 16.47	<0.001
DBP (mmHg)	76.94 ± 11.36	78.91 ± 10.66	76.06 ± 11.57	0.02
BMI (kg/m^2)	24.54 ± 3.57	26.70 [23.5, 28.4]	23.30 [21.8, 25.6]	<0.001
Waist circumference (cm)	84.99 ± 9.62	90 [83, 96]	82 [77, 88]	<0.001
Creatinine (mg/dL)	0.77 ± 0.42	0.71 [0.58, 0.86]	0.67 [0.57, 0.84]	0.26
FPG (mg/dL)	95.54 ± 22.32	101 [91, 120]	87 [81, 94]	<0.001
HDL-C (mg/dL)	54.51 ± 13.91	47 [40, 56]	55 [47, 66]	<0.001
HOMA-IR index	1.86 ± 1.39	2.84 [2.31, 3.83]	1.17 [0.83, 1.52]	<0.001
LDL-C (mg/dL)	118.47 ± 32.16	112.11 ± 29.83	121.31 ± 32.80	0.01
Total Cholesterol (mg/dL)	197.19 ± 35.69	191.46 ± 34.08	119.75 ± 36.16	0.03
Triglyceride (mg/dL)	121.20 ± 62.93	131 [105, 180]	96 [73, 126]	<0.001
WBC (1000/uL)	6.04 ± 1.59	6.3 [5.7, 7.4]	5.7 [4.8, 6.6]	<0.001
Men, *n* (%)	139 (34.9)	41 (33.3)	98 (35.6)	0.66
Current smoking, *n* (%)	42 (10.6)	12 (9.8)	30 (10.9)	0.73
HTN, *n* (%)	199 (50.0)	84 (68.3)	115 (41.8)	<0.001
DM, *n* (%)	77 (19.3)	48 (39.0)	29 (10.5)	<0.001
Hyperlipidemia, *n* (%)	259 (65.1)	93 (75.6)	166 (60.4)	0.003

Clinical characteristics are expressed as mean ± SD or median [Q1, Q3] for continuous variables and n (%) for categorical variables. P-value were derived from independent t-test and Mann-Whitney U test for continuous variables and chi-square test for categorical variables.
SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cell count; HTN, hypertension; DM, diabetes mellitus.

TABLE 2 | The correlation between HOMA-IR index and cardio-metabolic risk factors.

Variables	HOMA-IR index (*n* = 398)			
	Unadjusted		Adjusted for age	
	Pearson's coefficient	*p*-value	Pearson's coefficient	*p*-value
Age (year)	0.02	0.70	NA	NA
SBP (mmHg)	0.17	0.001	0.17	0.001
DBP (mmHg)	0.09	0.079	0.10	0.06
BMI (kg/m^2)	0.43	<0.001	0.433	<0.001
Waist circumference (cm)	0.41	<0.001	0.41	<0.001
FPG (mg/dL)	0.50	<0.001	0.50	<0.001
HDL-C (mg/dL)	−0.31	<0.001	−0.31	<0.001
LDL–C (mg/dL)	−0.10	0.06	−0.09	0.06
TG (mg/dL)	0.33	<0.001	0.33	<0.001
WBC (1000/uL)	0.37	<0.001	0.37	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; WBC, white blood cell count.

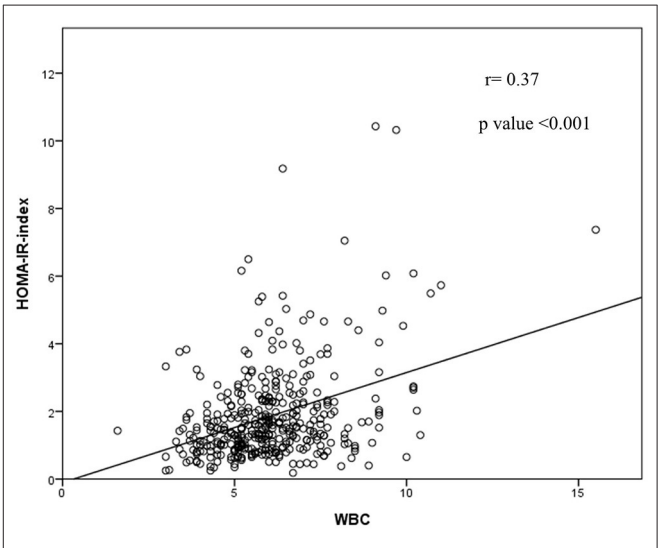

FIGURE 1 | Representation of the correlation analysis: there was a trend toward a positive correlation between HOMA-IR index and WBC.

a history of HTN. Diabetes mellitus (DM) was defined as a FPG level ≥ 126 mg/dL, the use of oral antidiabeticic drugs or insulin therapy, or a history of DM. Hyperlipidemia was defined as a LDL-C level ≥ 130 mg/dL, a TG level ≥ 150 mg/dL, a total cholesterol level ≥ 200 mg/dL, the use of lipid-lowering medication, or a history of hyperlipidemia (8).

TABLE 3 | Association between WBC levels and insulin resistance.

Variables	Odds ratio	95% C.I.	*p*-value
Model 1			
Sex (men vs. women)	0.68	0.42–1.10	0.12
WBC (1000/uL)	1.54	1.32–1.80	<0.001
Model 2			
Sex (men vs. women)	0.58	0.34–0.97	0.04
Age (year)	1.01	0.98–1.04	0.52
BMI (kg/m^2)	1.27	1.18–1.37	<0.001
WBC (1000/uL)	1.54	1.30–1.82	<0.001
Model 3			
Sex (men vs. women)	0.61	0.35–1.06	0.08
Age (year)	0.99	0.96–1.03	0.69
BMI (kg/m^2)	1.25	1.15–1.35	<0.001
HTN (yes vs. no)	1.87	1.11–3.16	0.02
DM (yes vs. no)	5.34	2.91–9.80	<0.001
Hyperlipidemia (yes vs. no)	1.38	0.79–2.40	0.26
WBC (1000/uL)	1.47	1.23–1.77	<0.001
Model 4			
Sex (men vs. women)	0.67	0.38–1.20	0.18
Age (year)	0.99	0.96–1.02	0.59
BMI (kg/m^2)	1.25	1.15–1.35	<0.001
Smoking (yes vs. no)	0.61	0.24–1.51	0.28
HTN (yes vs. no)	1.87	1.11–3.17	0.02
DM (yes vs. no)	5.40	2.93–9.93	<0.001
Hyperlipidemia (yes vs. no)	1.43	0.82–2.51	0.21
WBC (1000/uL)	1.50	1.25–1.81	<0.001

BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; WBC, white blood cell count; CI, confidence interval.

Definition of Insulin Resistance

HOMA-IR was expressed as fasting glucose (mmol/L) × fasting insulin (mU/mL)/22.5 (19). To define the main outcome variable of IR, the HOMA-IR cut-off value was set at 2.0.

Statistical Analysis

The sample size was determined using the G*power 3.1 software. The sample of this study comprised 398 subjects, which implied sufficient statistical power. All data on demographics and clinical characteristics were expressed as the mean ± standard deviation (SD) or median (Q1, Q3) for continuous variables and numbers (%) for categorical variables. Descriptive statistics were presented, and differences between the IR and non-IR groups were compared using the independent *t*-test and Mann–Whitney U test for continuous data and the chi-square test for categorical data. The correlations between the HOMA-IR index and cardiometabolic risk factors were assessed using Pearson's correlation test. In the multivariate analysis, binary logistic regression was used to adjust for covariates. Receiver operating characteristic (ROC) curves were plotted for WBC and IR. The area under the ROC curve (AUC) and optimal cut-off points were determined using Youden's index. Sensitivity, specificity, and AUC were calculated. Statistical analyses were performed using SPSS Statistics version 22 (IBM Corp., Armonk, NY, IMM Corp). All the statistical tests were two-sided with a statistical significance level defined as p-value < 0.05.

RESULTS

We recruited 398 participants. **Table 1** shows the general characteristics of the participants according to the IR and non-IR groups. Among the 398 subjects, 123 (30.9%) were in the IR group. There were 139 men (35%) and 259 women (65%), and the mean age was 64.43 ± 8.45 years. There were no significant differences between the IR and non-IR groups with respect to age, creatinine level, sex, and smoking status. Significant differences were found in SBP; DBP; BMI; WC; FPG, HDL-C, LDL-C, total cholesterol, TG, and WBC levels; DM; HTN; and hyperlipidemia. The overall percentage of participants reporting current smoking was 10.6%. The average BMI was 24.54 ± 3.57 kg/m^2; WC, 84.99 ± 9.62 cm; and, WBC count, 6.04 ±1.59 × 1,000/uL. The mean SBP and DBP were 129.57 ± 16.72 and 76.94 ± 11.36 mmHg, respectively. Overall, the mean FPG, HDL-C, LDL-C, total cholesterol, and TG levels were 95.54 ± 22.32, 54.51 ± 13.91, 118.47 ± 32.16, 197.19 ± 35.69 and 121.20 ± 62.93 mg/dL, respectively.

Table 2 demonstrates the correlations between the HOMA-IR index and the cardiometabolic risk factors. The WBC count remained positively associated with IR before and after adjusting for age. The WBC count showed a stronger correlation with HOMA-IR than most of the risk factors analyzed. **Figure 1** demonstrates the association of WBC and HOMA-IR index with a Pearson's correlation coefficient of 0.37.

The results of the multivariate logistic regression analyses are given in **Table 3**, where IR is the dependent variable and WBC count is the independent variable. The odds ratios (ORs) (95% confidence interval [CI]) of IR in terms of WBC count are presented in **Table 3**. In Model 1, the ORs (95% CI) were calculated after adjusting for sex. In Model 2, the ORs (95% CI) were calculated after adjusting for sex, age, and BMI. In Model 3, we examined the relationship between WBC count and IR after adjusting for additional confounding variables such as HTN, DM, and hyperlipidemia. In Model 4, we adjusted for sex, age, BMI, current smoking status, HTN, DM, and hyperlipidemia. In all the four models, BMI, DM, and WBC count were significantly associated with IR. In Model 4, BMI (adjusted odds ratio [aOR]: 1.25; 95% CI: 1.15–1.35; p <0.001), HTN (aOR: 1.87, 95% CI: 1.11–3.17; p-value <0.05), DM (aOR: 5.4, 95% CI: 2.93–9.93; p-value <0.001), and WBC count (aOR: 1.5, 95% CI: 1.25–1.81; p-value <0.001) were all significantly associated with IR.

The AUC of WBC for predicting IR was 0.67 (**Table 4**, **Figure 2**). The optimal cut-off point for WBC for predicting IR was 5.65 (1,000/uL), with a corresponding sensitivity and specificity of 75.6 and 49.8%, respectively.

DISCUSSION

In this cross-sectional community-based study, we found that a high WBC count was positively related to IR after adjusting

TABLE 4 | The areas under ROC curve (AUC), sensitivity, specificity by the optimized cut-off points for WBC in predicting HOMA-IR index.

Variables	AUC (95% CI)	*p* value	Cut-off point	Sensitivity	Specificity
WBC (1,000/uL)	0.67	<0.001	5.65	0.756	0.498

WBC, white blood cell count; ROC curve, receiver operating characteristic curve; CI, confidence interval.

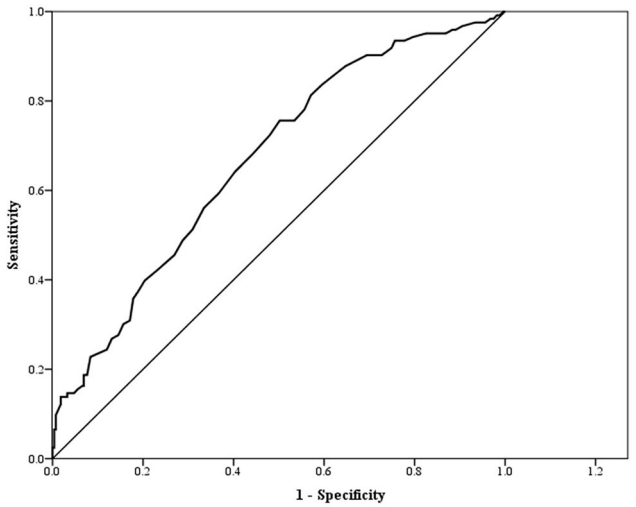

FIGURE 2 | ROC curve for WBC as a predictor of insulin resistance.

for potential confounding variables in the middle-aged and older populations in Taiwan.

Several studies have reported a positive correlation between WBC count and IR (16, 18, 20, 21), which is consistent with our findings. However, few studies have used the WBC count to identify the risk of IR. Park et al. (22) recently suggested that the WBC count can facilitate the identification of children and adolescents with IR. However, to our knowledge, it has not been used in adults.

Clinical prediction rules have become increasingly common in the improvement of healthcare delivery. This study aimed to use a simple biomarker as a clinical tool for evaluating IR in middle-aged and older populations. Therefore, we used logistic regression to explore the association between IR and the WBC count. Previous studies have shown that WBC count is a risk factor for metabolic syndrome (23), T2DM (24) and cardiovascular disease (25). It has been suggested that the link between WBC count and cardiovascular disease may be represented by a decrease in insulin sensitivity (25, 26). The association between WBC count and IR was significant in the middle-aged and older populations in Taiwan, even after adjusting for multiple covariates.

In the present study, IR was measured by HOMA-IR, an extensively validated tool to quantify IR, and our cut-off value (2.0) was similar to that of a study in 1,156 Caucasians (2.29) (27, 28). The covariates (BMI, WC, FPG level, HDL-C level, TG level, and WBC count) were all significantly associated with IR, regardless of age, through Pearson's correlation coefficient. In our clinical prediction models, the WBC count remained significantly associated with IR after adjusting for covariates such as age, sex, BMI, current smoking status, HTN, DM, and hyperlipidemia. This result reinforces the relationship between IR and WBC count; therefore, we suggest that WBC count could be used to identify IR.

In previous studies, Chao et al. (29) found that the threshold value of WBC count for predicting the future development of metabolic syndrome was 5 × 1,000/uL. Oda et al. (30) reported that the WBC count threshold values for predicting metabolic syndrome were 5 × 1,000/uL for women and 5.63 × 1,000/uL for men. Twig et al. (21) reported that patients with WBC counts above 6.9 × 1,000/uL were at a 52% increased risk of diabetes as compared to those in the lowest quintile. In our study, the WBC count threshold value for identifying IR in middle-aged and older Taiwanese was 5.65 × 1,000/uL.

In our study, the AUC value for identifying IR (as measured by HOMA-IR) with WBC count was 0.67, and the optimal threshold was 5.65 × 1,000/uL, with a corresponding sensitivity and specificity of 75.6% and 49.8%, respectively. We considered WBC count to be a potential marker for IR assessment. We suggest that WBC count could be an alternative marker used in combination with HOMA-IR to identify IR individuals in this population.

Even though we obtained an AUC of 0.67, which showed sufficient accuracy of the marker (31),we would still recommend using the WBC count alone for IR assessment with caution, as the WBC count may be influenced by an array of factors including acute infection, bone marrow disorders, and certain medications (32).

Our study had several strengths. First, the features of this study include a clear design, a sufficient sample size, a comprehensive inclusion of relevant confounders, and a well-performed data analysis. Second, the novelty of this study was, from a community approach, to report different cut-off values of WBC count among the middle-aged and older populations to better predict insulin resistance in these two specific age groups. Third, no similar studies have search investigated this topic in a community-dwelling population in Taiwan. There are several limitations to our study. First, there was lack of information on alcohol intake, regular physical exercise, and family history of diabetes in the study population. Second, the cross-sectional design used in this study made it difficult to explore the causal relationship between WBC count and IR in the study population. Third, all the participants were volunteers from a community in northern Taiwan, which may have led to a possible selection bias.

In conclusion, elevated WBC was significantly associated with IR in the middle-aged and older populations in Taiwan.

However, WBC count may not only serve as a biomarker for early identification of IR but may also be used as a surrogate marker for excluding IR. Future research is warranted to further investigate the use of WBCs for predicting IR in a larger 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 Chang Gung Medical Foundation Institutional Review Board (102-2304B). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

J-YC contributed to the conception and design of the research. J-YC and M-TT were involved in data acquisition, analysis and interpretation, drafted, and revised the manuscript critically for important intellectual content. Y-HC and Y-CL were involved in data cleaning and follow-up. All authors have read and agreed to the published version of the manuscript.

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Dose-Response Relationship of Uric Acid With Fasting Glucose, Insulin, and Insulin Resistance in a United States Cohort of 5,148 Non-diabetic People

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Background: There is a limited number of studies on the dose-response relationship between serum uric acid and impaired glucose metabolism in people without diabetes, and no large-scale research exploring the relationship in women without diabetes is based on menopausal status. Consequently, the present study aimed to investigate the above relationship in United States adults without diabetes.

Materials and Methods: Data from 2,498 men and 2,650 women aged ≥20 years were obtained from the National Health and Nutrition Examination Survey 2011–2016 conducted in the United States. Binary logistic regression analysis was applied to evaluate the association between uric acid and impaired glucose metabolism. Restricted cubic spline analysis, sensitivity analysis, and stratified analysis by menopausal status were performed to explore the above relationships.

Results: A positive correlation was found between uric acid and the risk of insulin resistance in all participants ($P < 0.05$). In binary logistic regression analysis, after adjusting for confounding factors, compared with the lowest quartile of uric acid, the odds ratio (95% confidence intervals) of insulin resistance in the highest quartile was 1.9 (1.1–3.1) and 2.2 (1.2–4.3) in men and women, respectively. A significant positive relationship was also observed between uric acid and impaired fasting glucose and hyperinsulinemia in women, while in men, uric acid was positively associated with the risk of hyperinsulinemia but not impaired fasting glucose. Restricted cubic spline showed that the odds ratios of insulin resistance and hyperinsulinemia increased with elevating uric acid levels in both men and women. When stratified by menopause, the association remained significant in pre-menopausal women aged ≥20, but insignificant in post-menopausal women.

Conclusion: Uric acid was positively associated with the risk of impaired glucose metabolism in a cohort of United States adults, and uric acid increased the risk of insulin resistance in pre-menopausal, but not in post-menopausal women.

Keywords: uric acid, insulin resistance, fasting glucose, hyperinsulinemia, menopausal status, NHANES

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INTRODUCTION

Uric acid (UA) is the end product of purine nucleotide metabolism. Approximately, two-third of UA is excreted by the kidneys and one-third by the gastrointestinal tract, and its synthesis and excretion are balanced under physiological conditions (1, 2). Hyperuricemia is the precursor of gout that can occur due to overproduction or underexcretion of serum uric acid (SUA). In addition to gout, numerous research studies have suggested the clinical significance of SUA beyond the rheumatologic field (3), such as impaired glucose metabolism, abnormal lipid metabolism, and higher prevalence of obesity, hypertension, and metabolic syndrome (4–10). Previous studies have also suggested a bidirectional causal effect between SUA and insulin resistance (IR) (11). SUA was found to affect the function of islet β cells and was inversely associated with insulin sensitivity (11, 12).

Insulin exerts its physiological function through a cascade of signaling transduction by enhancing glucose disposal in insulin-sensitive tissues. IR is defined as the inability of insulin to optimally stimulate the transport of glucose into cells (13). It is also considered a hallmark of metabolic syndrome and an important pathogenic factor of type 2 diabetes mellitus (11, 14). Impaired fasting glucose and compensatory hyperinsulinemia are accompanying characteristics of IR. Moreover, IR is closely associated with dyslipidemia, coronary artery disease, and hypertension (15), while abdominal obesity, acanthosis nigricans, and acne are considered their major clinical features (16). In addition, restricting calorie intake and exercising are associated with improved insulin sensitivity, while aging, smoking, and inactive physical activity are positively associated with the risk of IR (16).

Accumulating evidence demonstrated that SUA is associated with impaired glucose metabolism; however, these results appear to be inconsistent. Some clinical studies found that elevated SUA was associated with a higher risk of IR, hyperinsulinemia, fasting plasma glucose, and HbA1c level (17, 18). However, in their study on 605 newly diagnosed type 2 diabetes patients, Ma et al. found that SUA was inversely correlated with HbA1c in the high insulin group, while no associations were found in the low insulin group (19).

Previous studies on the association between SUA and glucose metabolism mostly included prediabetic or diabetic patients. Some limited small-scale studies investigated the above association in United States adults without diabetes, and no large-scale research explored the above relationship in women without diabetes based on menopausal status. Therefore, the present study included a nationally representative cohort of United States adults without diabetes whose data were obtained from the National Health and Nutrition Examination Survey (NHANES) 2011–2016 to explore the dose-response relationship between SUA and IR, impaired fasting glucose, and hyperinsulinemia. We performed restricted cubic spline analysis and stratified analysis by menopausal status to explore the above relationship with a large-scale nationwide sample for the first time to provide a valuable reference for the impaired glucose metabolism and further study of IR in women with different menopausal statuses.

Abbreviations: NHANES, National Health and Nutrition Examination Surveys; SUA, serum uric acid; BMI, body mass index; ORs, odds ratios; CIs, confidence intervals; eGFR, estimation of the glomerular filtration rate; ROS, reactive oxygen species; PIR, poverty income ratio; IFG, Impaired fasting glucose; HOMA-IR, homeostasis model assessment of insulin resistance; IRS1, insulin receptor substrate 1; Akt, protein kinase B.

MATERIALS AND METHODS

Data Source and Study Population

The NHANES, which collects the health and nutritional information of the United States population every 2 years, is conducted by the Centers for Disease Control and Prevention of America. Through a multistage, stratified sampling design, NHANES included a representative sample of non-institutionalized United States civilians. After a detailed in-home interview, a physical examination and blood and urine specimens were obtained at specially equipped mobile examination centers (20). Written informed consent was obtained before the interview, and examination stages from all participants and all data were de-identified by the National Center for Health Statistics before being made publicly available.

A total of 29,902 adult participants were enrolled in the NHANES between 2011 and 2016. Exclusion criteria were the following: (1) age <20 years (n = 12,824); (2) participants whose SUA data (n = 1,718) and serum fasting glucose and insulin data (n = 8,061) were missing; (3) self-reported cancer or malignancy (n = 670); (4) being pregnant or breastfeeding (n = 74); (5) self-reported diabetes, fasting glucose ≥ 7.0 mmol/L or 2-h glucose of oral glucose tolerance test ≥ 11.1 mmol/L, HbA1C ≥ 6.5%, and receive insulin or hypoglycemic drugs now (n = 1,407). Eventually, 2,498 men and 2,650 women were included in our study. The flow chart of the screening process is shown in **Figure 1**.

Study Variables

Variables in this study included age, race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other race), body mass index (BMI) (normal: <25 kg/m^2; overweight: 25–30 kg/m^2; and obesity: ≥ 30 kg/m^2) (21), education level (Less than 9th grade, 9–11th grade, High school graduate, College degree, and College graduate or above), waist circumference, and estimation of the glomerular filtration rate (eGFR) [eGFR = 175 × standardized Scr$^{-1.154}$ × age$^{-0.203}$ × 1.212 (if black) × 0.742 (if women)](22). The poverty income ratio (PIR) was used to define income, categorized as less than 0.99 and 1 or more; a PIR < 1.0 represented a person living under the poverty line. Total cholesterol, triglyceride, smoking status (smoked at least 100 cigarettes in life or not), and drinking status (had at least 12 alcohol drinks/1 year) were also included in the present study. A history of hypertension is defined as the self-reported diagnosis of hypertension by a physician. Urate-lowering therapy was also adjusted in our study. NHANES questions, *"In the past 30 days, have you used or taken medication for which a prescription is*

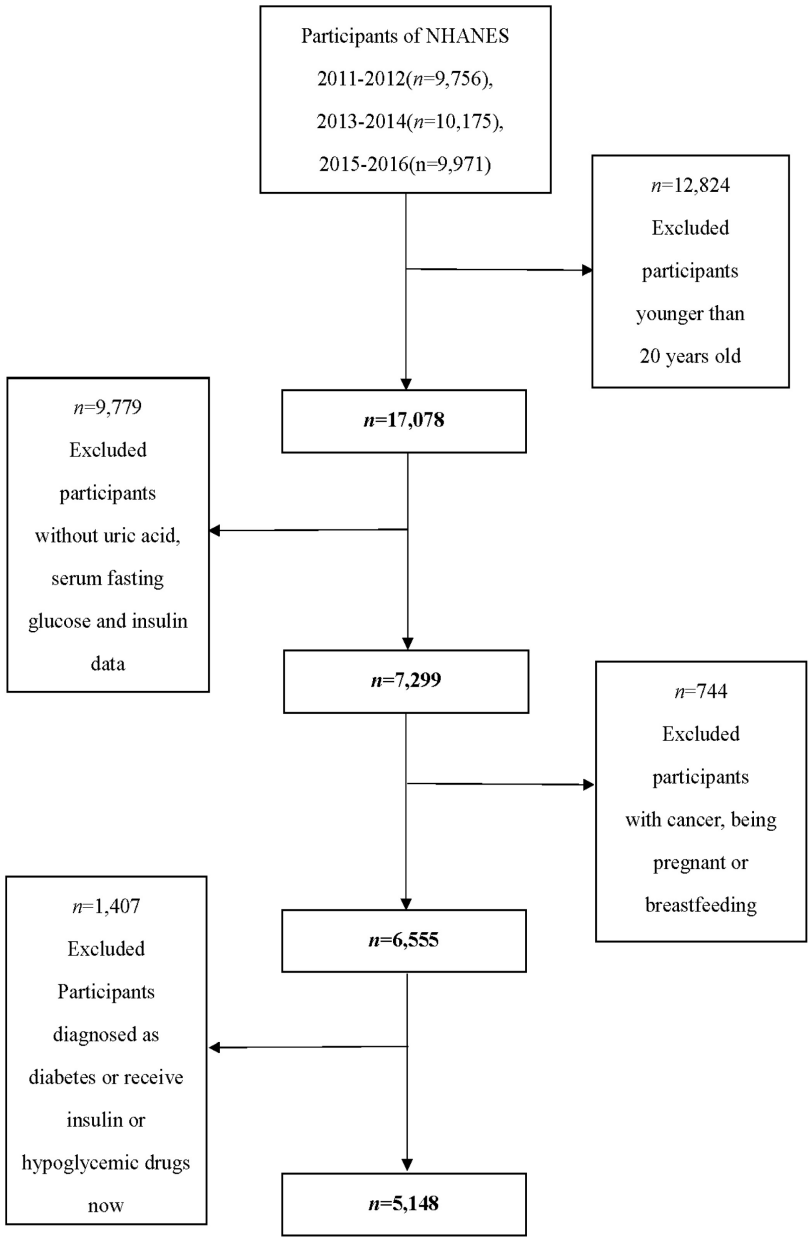

FIGURE 1 | Flow chart of the screening process for the selection of eligible participants.

needed?" and *"Generic drug name,"* revealed that 10 women and 29 men were using uric lowering therapy (allopurinol, febuxostat, and probenecid).

Definitions

The homeostasis model assessment of IR (HOMA-IR) is a common indirect index for the assessment of IR. HOMA-IR = [fasting insulin (mU/L) × fasting glucose (mmol/L)]/22.5 (23). IR was defined as HOMA-IR ≥ 75th percentile (HOMA-IR ≥ 3.55 for men and ≥ 3.45 for women) by gender in our study population (24). Impaired fasting glucose (IFG) was defined as 6.1 mmol/L ≤ fasting plasma glucose < 7.0 mmol/L (25). Hyperinsulinemia was defined as serum insulin ≥ 75th percentile by gender (Insulin ≥ 14.15 for men and ≥ 14.03 for women) (26). Menopause was defined by answering "no" to the question "Have you had at least one menstrual period in the past 12 months?" or age ≥ 55 (27).

Statistical Analysis

All statistical analyses were conducted with SPSS 23, STATA 15.0, and R 4.1.0. The normality of the continuous variable was tested with the Kolmogorov–Smirnov normality test. Normally distributed variables were described with mean ± SD, while non-normally distributed continuous variables were described

with median (interquartile range). The median values among different SUA groups were compared with the Kruskal–Wallis test. The percentages of categorical variables among different SUA groups were compared with the Chi-square test. The Bonferroni test was used for the intergroup comparison. As the SUA level substantially differed between men and women, the analyses were performed separately by gender. SUA levels in binary logistic regression analyses were modeled in quartiles: Men groups: Q1 (uric acid $\leq$ 309.30 μmol/L), Q2 (309.30 < uric acid $\leq$ 356.90 μmol/L), Q3 (356.90 < uric acid $\leq$ 404.50 μmol/L), and Q4 (uric acid > 404.50 μmol/L); Women groups: Q1 (uric acid $\leq$ 232.00 μmol/L), Q2 (232.00 < uric acid $\leq$ 273.60 μmol/L), Q3 (273.60 < uric acid $\leq$ 321.20 μmol/L), and Q4 (uric acid > 321.20 μmol/L). The lowest quartile (Q1) group was used as the reference group. Binary logistic regression analysis examined the association between SUA and IR, impaired fasting glucose, and hyperinsulinemia. We compared the clinical characteristics of the study population with or without IR, and the covariates with significant differences between the two groups were included in the full-adjusted Model 2. Finally, the race was adjusted in Model 1, and Model 2 was additionally adjusted for BMI, waist circumference, drinking status, education level, hypertension, total cholesterol, triglyceride, and urate-lowering therapy.

Logistic regression analysis was performed to calculate the odds ratio (OR) values per SD increase in SUA. We also performed linear regression analysis to assess the association between SUA and HOMA-IR. Stratified analysis and trend tests were used for female participants based on menopausal status, as the SUA levels increased substantially after menopause (28). Participants with no available information about menopause were excluded from the stratified analysis. In addition to menopause, stratified analysis based on BMI (normal: < 25 kg/m^2; overweight: between 25 and 30 kg/m^2;

TABLE 1 | Clinical characteristics of the study population disaggregated by quartiles of serum uric acid level.

Serum uric acid quartile	Q1	Q2	Q3	Q4	*P*-value
Number of subjects	635	685	567	611	
Age (year)[b]	44 (27)	42 (26.5)	42 (24)	42 (28)	0.221
Race (%)[a]					0.103
Mexican American	95 (15.0)	93 (13.6)	88 (15.5)	62 (10.1)	
Other Hispanic	70 (11.0)	85 (12.4)	65 (11.5)	55 (9.0)	
Non-Hispanic White	240 (37.8)	266 (38.8)	222 (39.2)	246 (40.3)	
Non-Hispanic Black	127 (20.0)	116 (16.9)	98 (17.3)	129 (21.1)	
Other race	103 (16.2)	125 (18.2)	94 (16.6)	119 (19.5)	
Education level (%) [a]					< 0.01
Less than 9th grade	71 (11.2)	56 (8.2)	48 (8.5)	30 (4.9)	
9–11th grade	92 (14.5)	100 (14.6)	87 (15.3)	92 (15.1)	
High school graduate	160 (25.2)	139 (20.3)	141 (24.9)	143 (23.4)	
College or AA degree	159 (25.0)	211 (30.8)	157 (27.7)	165 (27.0)	
College graduate or above	153 (24.1)	179 (26.1)	134 (23.6)	181 (29.6)	
Waist circumference (cm)[b]	91.6 (17.8)	95.5 (17.1)	99.3 (15.8)	102.2 (20.5)	< 0.01
Body mass index (kg/m^2)[b]	24.9 (5.75)	26.5 (6.03)	28.2 (6.20)	29.3 (7.6)	< 0.01
Cholesterol (mmol/L)[b]	4.65 (1.37)	4.81 (1.34)	4.97 (1.30)	5.04 (1.35)	< 0.01
Triglyceride (mmol/L)[b]	0.96 (0.70)	1.12 (0.79)	1.28 (1.01)	1.48 (1.24)	< 0.01
Creatinine (μmol/L)[b]	79.6 (19.5)	83.1 (17.7)	84.9 (19.5)	88.4 (20.3)	< 0.01
eGFR (mL/min per 1·73m^2)[b]	97.27 (27.68)	92.33 (24.04)	90.66 (27.90)	84.91 (25.84)	< 0.01
Insulin (mU/L)[b]	7.10 (6.04)	7.94 (7.68)	10.03 (9.23)	11.92 (12.16)	< 0.01
Fasting glucose (mmol/L)[b]	5.49 (0.67)	5.49 (0.61)	5.50 (0.67)	5.61 (0.67)	< 0.01
HOMA-IR[b]	1.74 (1.56)	1.96 (1.89)	2.45 (2.42)	3.05 (3.29)	< 0.01
Insulin resistance (%)[a]	81 (12.8)	128 (18.7)	172 (30.3)	243 (39.8)	< 0.01
Poverty income ratio <1 (%)[a]	145 (25.5)	139 (22.0)	106 (20.2)	92 (16.3)	< 0.01
Serum uric acid (μmol/L)[b]	279.6 (35.7)	339.0 (17.9)	380.7 (23.8)	446.1 (59.5)	< 0.01
Glycohemoglobin (%)[b]	5.4 (0.5)	5.4 (0.4)	5.4 (0.4)	5.5 (0.6)	< 0.01
Hypertension (%)[a]	149 (23.5)	149 (21.8)	154 (27.2)	221 (36.2)	< 0.01
Had at least 12 alcohol drinks/year (%)[a]	455 (78.6)	566 (87.5)	444 (86.2)	483 (85.3)	< 0.01
Smoked at least 100 cigarettes in life (%)[a]	342 (53.9)	342 (49.9)	296 (52.2)	317 (51.9)	0.559

NHANES 2011–2016 (Men = 2,498).

Data are number of subjects (percentage) or medians (interquartile ranges).

[a]*Chi-square test was used to compare the percentage among participants in different groups.*

[b]*Kruskal–Wallis test was used to compare the median values among participants in different groups.*

Serum uric acid quartiles: Q1 (uric acid ≤ 309.30 μmol/L), Q2 (309.30 < uric acid ≤ 356.90 μmol/L), Q3 (356.90 < uric acid ≤ 404.50 μmol/L), and Q4 (uric acid > 404.50 μmol/L).

and obesity: ≥ 30 kg/m^2), waist circumference (cutoff value for American: 102 cm for men and 88 cm for women), serum triglyceride (cutoff value: 1.7 mmol/L), total cholesterol (cutoff value: 5.2 mmol/L) (29), drinking status (Yes/No), education levels (college and above/high school and below), and hypertension (Yes/No) were also performed. Subsequently, a sensitivity analysis was performed by excluding participants without metabolic syndrome to minimize the influence of metabolic syndrome. Restricted cubic spline analysis with 3 knots of the SUA levels was used to characterize the dose-response relationship in the logistic regression Model 2. The function "lrm" and function "rcs" in the "rms" package of R 4.1.0. were used to fit the independent and dependent variables. The reference values were automatically determined by "rcs" function. The function "predict" was used to calculate the ORs (95% CIs) and reference point (OR = 1.0) of SUA. A two-sided $p < 0.05$ was considered statistically significant.

RESULTS

A total of 5,148 participants (2,498 men, 2,650 women) were included in the study and categorized into five racial groups: Mexican American (n = 682), Other Hispanic (n = 567), Non-Hispanic White (n = 2,000), Non-Hispanic Black (n = 1,020), and other races (n = 879). The mean age was 45.21 ± 16.53 years, and the mean SUA was 320.93 ± 81.80 μmol/L. There were 20.1% of male participants and 12.9% of female participants who met the hyperuricemia criteria; 11.7% of all participants were with an SUA concentration ≥420 μmol/L. The clinical characteristics of individuals from different SUA groups are shown in **Tables 1**, **2**. A greater proportion of participants with IR or hypertension belonged to the highest quartile of SUA level; with the increasing of SUA quartiles, the median of eGFR gradually declined, while the median of BMI, waist circumference, cholesterol, triglyceride,

TABLE 2 | Clinical characteristics of the study population disaggregated by quartiles of serum uric acid level.

Serum uric acid quartile	Q1	Q2	Q3	Q4	*P*-value
Number of subjects	663	694	648	645	
Age (year)[b]	41 (23)	42 (25)	44 (26)	52 (24)	0.058
Race (%)[a]					< 0.01
Mexican American	108 (16.3)	90 (13.0)	77 (11.9)	69 (10.7)	
Other Hispanic	89 (13.4)	84 (12.1)	67 (10.3)	52 (8.1)	
Non-Hispanic White	231 (34.8)	263 (37.9)	238 (36.7)	294 (45.6)	
Non-Hispanic Black	139 (21.0)	131 (18.9)	140 (21.6)	140 (21.7)	
Other race	96 (14.5)	126 (18.2)	126 (19.4)	90 (14.0)	
Education level (%)[a]					< 0.01
Less than 9th grade	56 (8.4)	63 (9.1)	57 (8.8)	43 (6.7)	
9–11th grade	83 (12.5)	66 (9.5)	73 (11.3)	75 (11.6)	
High school graduate	116 (17.5)	121 (17.4)	119 (18.4)	146 (22.6)	
College degree	203 (30.6)	209 (30.1)	216 (33.3)	225 (34.9)	
College graduate or above	205 (30.9)	235 (33.9)	183 (28.2)	156 (24.2)	
Waist circumference (cm)[b]	86.2 (16.2)	91.0 (19.3)	96.3 (22.0)	102.8 (22.3)	< 0.01
Body mass index (kg/m^2)[b]	24.9 (6.6)	26.9 (8.6)	28.6 (9.6)	31.3 (11.0)	< 0.01
Cholesterol (mmol/L)[b]	4.71 (1.26)	4.81 (1.24)	4.94 (1.27)	5.12 (1.39)	0.085
Triglyceride (mmol/L)[b]	0.84 (0.57)	0.93 (0.67)	1.03 (0.72)	1.30 (0.96)	< 0.01
Creatinine (μmol/L)[b]	60.1 (15.9)	61.9 (15.0)	64.5 (18.4)	68.1 (21.2)	< 0.01
eGFR (mL/min per 1·73m^2)[b]	100.18 (32.10)	94.81 (27.45)	91.96 (30.86)	83.53 (35.13)	< 0.01
Insulin (mU/L)[b]	7.06 (5.84)	8.16 (7.00)	9.96 (8.66)	11.66 (11.00)	< 0.01
Fasting glucose (mmol/L)[b]	5.22 (0.56)	5.27 (0.67)	5.38 (0.61)	5.50 (0.78)	< 0.01
HOMA-IR[b]	1.64 (1.37)	1.89 (1.84)	2.37 (2.24)	2.84 (3.00)	< 0.01
Insulin resistance (%)[a]	82 (12.4)	131 (18.9)	180 (27.8)	270 (41.9)	< 0.01
Poverty income ratio <1 (%)[a]	166 (27.2)	160 (24.7)	139 (23.3)	149 (25.3)	0.485
Serum uric acid (μmol/L)[b]	208.2 (35.7)	255.8 (23.8)	297.4 (23.8)	362.8 (59.5)	< 0.01
Glycohemoglobin (%)[b]	5.4 (0.5)	5.4 (0.5)	5.4 (0.5)	5.5 (0.5)	0.360
Hypertension (%) [a]	136 (20.5)	159 (22.9)	199 (30.7)	293 (45.4)	< 0.01
Had at least 12 alcohol drinks/year (%)[a]	359 (62.4)	402 (66.4)	363 (63.4)	344 (59.9)	0.138
Smoked at least 100 cigarettes in life (%)[a]	207 (31.2)	211 (30.4)	204 (31.5)	231 (35.8)	0.149

NHANES 2011–2016 (Women = 2,650).

Data are number of subjects (percentage) or medians (interquartile ranges).

[a]Chi-square test was used to compare the percentage among participants in different groups.

[b]Kruskal–Wallis test was used to compare the median values among participants in different groups.

Serum uric acid quartiles: Q1 (uric acid ≤ 232.00 μmol/L), Q2 (232.00 < uric acid ≤ 273.60 μmol/L), Q3 (273.60 < uric acid ≤ 321.20 μmol/L), and Q4 (uric acid > 321.20 μmol/L).

serum insulin, creatinine, and HOMA-IR gradually increased in both men and women. Among men, the proportion of those living under the poverty line gradually declined with the increase of SUA quartiles. The clinical characteristics of individuals with or without IR are shown in **Table 3**. The waist circumference, BMI, triglyceride, total cholesterol level, glycohemoglobin, and prevalence of hypertension were significantly higher in the IR group.

The results of binary logistic regression analysis are presented in **Tables 4–8**. In men, the crude ORs with 95% confidence intervals (CIs) of IR was 1.6 (1.1–2.3), 3.2 (2.2–4.8), and 4.6 (3.3–6.6) in Q2, Q3, and Q4, respectively, vs. Q1 of SUA. In Model 1, after adjusting for race, the adjusted ORs with 95% CIs were 1.6 (1.1–2.3), 3.2 (2.1–4.8), and 4.8 (3.4–6.7) in Q2, Q3, and Q4, respectively, vs. Q1 of SUA. In Model 2, the multivariate-adjusted ORs with 95% CIs were 1.2 (0.7–1.9), 1.9 (1.1–3.4), and 1.9 (1.1–3.1) in Q2, Q3, and Q4, respectively, vs. Q1 of SUA. In women, the crude ORs with 95% CIs of IR were 1.7 (1.2–2.5), 2.3 (1.4–3.6), and 5.9 (3.8–9.1) in Q2, Q3, and Q4, respectively, vs. Q1 of SUA. In Model 1, the adjusted ORs with 95% CI were 1.9 (1.3–2.7), 2.5 (1.5–3.9), and 6.6 (4.2–10.4) in Q2, Q3, and Q4, respectively,

TABLE 3 | Clinical characteristics of the study population in insulin resistance and non-insulin resistance group.

Characteristics	Insulin resistance group	Non-insulin resistance group	*P*-value
Number of subjects	1287	3861	
Age (year)[b]	43 (26)	43 (27)	0.855
Race (%)[a]			< 0.01
Mexican American	231 (17.9)	451 (11.7)	
Other Hispanic	152 (11.8)	415 (10.7)	
Non-Hispanic White	466 (36.2)	1534 (39.7)	
Non-Hispanic Black	279 (21.7)	741 (19.2)	
Other race	159 (12.4)	720 (18.6)	
Education level (%)[a]			< 0.01
Less than 9th grade	119 (9.2)	305 (7.9)	
9–11th grade	188 (14.6)	480 (12.4)	
High school graduate	275 (21.4)	810 (21.0)	
College or AA degree	418 (32.5)	1127 (29.2)	
College graduate or above	287 (22.3)	1139 (29.5)	
Waist circumference (cm)[b]	108 (19.7)	91.7 (18.1)	< 0.01
Body mass index (kg/m^2)[b]	32.5 (8.8)	25.9 (6.5)	< 0.01
Cholesterol (mmol/L)[b]	4.91 (1.35)	4.86 (1.31)	0.029
Triglyceride (mmol/L)[b]	1.502 (1.14)	0.982 (0.711)	< 0.01
Creatinine (μmol/L)[b]	73.37 (23.87)	73.37 (25.63)	0.578
eGFR (mL/min per 1·73m^2) [b]	92.42 (31.37)	92.50 (28.65)	0.793
Poverty income ratio <1 (%)[a]	292 (25.1)	804 (22.5)	0.072
Serum uric acid (μmol/L)[b]	345.0 (113.0)	303.3 (101.1)	< 0.01
Glycohemoglobin (%)[b]	5.6 (0.5)	5.4 (0.5)	< 0.01
Hypertension (%)[a]	491 (38.2)	969 (25.1)	< 0.01
Had at least 12 alcohol drinks/year (%)[a]	810 (70.6)	2606 (74.8)	< 0.01
Smoked at least 100 cigarettes in life (%)[a]	537 (41.7)	1613 (41.8)	0.974

NHANES 2011–2016 (n = 5,148).
Data are number of subjects (percentage) or medians (interquartile ranges).
[a]Chi-square test was used to compare the percentage of participants with and without insulin resistance.
[b]Mann–Whitney U-test was used to compare the median values between participants with and without insulin resistance.

TABLE 4 | Weighted odds ratios (95% confidence intervals) for insulin resistance (HOMA-IR) of participants across quartiles of serum uric acid (Men = 2,498, women = 2,650).

	Case/Participants	Crude[a]	Model 1[a]	Model 2[a]
Men[†]				
Q1	635/2,498	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Q2	685/2,498	1.6 (1.1–2.3) *	1.6 (1.1–2.3) *	1.2 (0.7–1.9)
Q3	567/2,498	3.2 (2.2–4.8) **	3.2 (2.1–4.8) **	1.9 (1.1–3.4) *
Q4	611/2,498	4.6 (3.3–6.6) **	4.8 (3.4–6.7) **	1.9 (1.1–3.1) *
Women[†]				
Q1	663/2,650	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Q2	694/2,650	1.7 (1.2–2.5) **	1.9 (1.3–2.7) **	1.3 (0.7–2.5)
Q3	648/2,650	2.3 (1.4–3.6) **	2.5 (1.5–3.9) **	1.3 (0.6–2.5)
Q4	645/2,650	5.9 (3.8–9.1) **	6.6 (4.2–10.4) **	2.2 (1.2–4.3) *

[a]Calculated using binary logistic regression.
[†]Men: Q1 (uric acid ≤ 309.30 μmol/L), Q2 (309.30 < uric acid ≤ 356.90 μmol/L), Q3 (356.90 < uric acid ≤ 404.50 μmol/L), and Q4 (uric acid > 404.50 μmol/L). Women: Q1 (uric acid ≤ 232.00 μmol/L), Q2 (232.00 < uric acid ≤ 273.60 μmol/L), Q3 (273.60 < uric acid ≤ 321.20 μmol/L), and Q4 (uric acid > 321.20 μmol/L).
Model 1 adjusted for race.
Model 2 adjusted for race, body mass index, waist circumference, drinking status, education level, hypertension, serum triglyceride, total cholesterol, and urate-lowering therapy.
**P < 0.05.*
***P < 0.01.*

TABLE 5 | Weighted odds ratios (95% confidence intervals) for impaired fasting glucose of participants across quartiles of serum uric acid (Men = 2,498, women = 2,650).

	Case/Participants	Crude[a]	Model 1[a]	Model 2[a]
Men[†]				
Q1	635/2,498	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Q2	685/2,498	0.8 (0.6–1.29)	0.8 (0.5–1.3)	0.8 (0.5–1.4)
Q3	567/2,498	1.7 (1.1–2.56) *	1.7 (1.1–2.6) *	1.2 (0.7–2.1)
Q4	611/2,498	2.1 (1.4–3.03) **	2.1 (1.4–3.1) **	1.4 (0.8–2.2)
Women[†]				
Q1	663/2,650	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Q2	694/2,650	1.5 (0.8–2.9)	1.5 (0.8–2.9)	1.3 (0.6–3.1)
Q3	648/2,650	1.8 (1.0–3.3)	1.8 (1.0–3.2)	1.5 (0.7–3.1)
Q4	645/2,650	4.9 (2.8–8.7) **	4.8 (2.7–8.5) **	2.7 (1.4–5.5) **

[a]Calculated using binary logistic regression.
[†]Men: Q1 (uric acid ≤ 309.30 μmol/L), Q2 (309.30 < uric acid ≤ 356.90 μmol/L), Q3 (356.90 < uric acid ≤ 404.50 μmol/L), and Q4 (uric acid > 404.50 μmol/L). Women: Q1 (uric acid ≤ 232.00 μmol/L), Q2 (232.00 < uric acid ≤ 273.60 μmol/L), Q3 (273.60 < uric acid ≤ 321.20 μmol/L), and Q4 (uric acid > 321.20 μmol/L).
Model 1 adjusted for race.
Model 2 adjusted for race, body mass index, waist circumference, drinking status, education level, hypertension, serum triglyceride, total cholesterol, and urate-lowering therapy.
**P < 0.05.*
***P < 0.01.*

vs. Q1 of SUA. In Model 2, the multivariate-adjusted ORs with 95% CIs were 1.3 (0.7–2.5), 1.3 (0.6–2.5), and 2.2 (1.2–4.3) in Q2, Q3, and Q4, respectively, vs. Q1 of SUA. The dose-response relationships between SUA and IR are presented in **Figures 2A,B**, **W**hile uric acid levels were positively associated with the risk of IR in both men and women ($P < 0.01$, P for non-linearity = 0.22 and 0.57, respectively). The reference points (OR = 1) of SUA in the restricted cubic spline analysis were 357.86 μmol/L for men and 275.01 μmol/L for women, respectively.

The results of binary logistic regression analysis between SUA levels and the risk of impaired fasting glucose are shown in **Table 5**. In the full-adjusted Model 2, the ORs with 95% CIs were 0.8 (0.5–1.4), 1.2 (0.7–2.1), and 1.4 (0.8–2.2) in Q2, Q3, and Q4, respectively, vs. Q1 of SUA in men, and the ORs with 95%CIs were 1.3 (0.6–3.1), 1.5 (0.7–3.1), and 2.7 (1.4–5.5) in Q2, Q3, and Q4, respectively, vs. Q1 of SUA in women. The results of the restricted cubic spline analysis between SUA and the risk of impaired fasting glucose are shown in **Figures 2C,D**. SUA levels were positively associated with the risk of IFG in women ($P < 0.01$) but not in men ($P = 0.38$).

The results of binary logistic regression analysis between SUA levels and the risk of hyperinsulinemia are presented in **Table 6**. In men, the ORs with 95% CIs were 1.5 (1.0–2.2), 2.8 (1.8–4.3), and 4.5 (3.1–6.5) in Q2, Q3, and Q4, respectively, vs. Q1 of SUA in Model 1, while in Model 2, the ORs with 95% CIs were 1.2 (0.7–1.9), 1.6 (0.9–2.9), and 1.8 (1.1–2.8) in Q2, Q3, and Q4, respectively, vs. Q1 of SUA. In women, the ORs with 95% CIs were 1.8 (1.3–2.6), 2.4 (1.5–3.8), and 5.9 (4.0–8.9) in Q2, Q3, and Q4, respectively, vs. Q1 of SUA in Model 1, while in the full-adjusted Model 2, the ORs with 95% CIs were 1.3 (0.7–2.4), 1.3 (0.7–2.4), and 2.0 (1.1–3.8) in Q2, Q3, and Q4, respectively, vs. Q1 of SUA. The results of the restricted cubic spline analysis

TABLE 6 | Weighted odds ratios (95% confidence intervals) for hyperinsulinemia of participants across quartiles of serum uric acid (Men = 2,498, women = 2,650).

	Case/Participants	Crude[a]	Model 1[a]	Model 2[a]
Men[†]				
Q1	635/2,498	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Q2	685/2,498	1.5 (1.0–2.2) *	1.5 (1.0–2.2) *	1.2 (0.7–1.9)
Q3	567/2,498	2.8 (1.8–4.3) **	2.8 (1.8–4.3) **	1.6 (0.9–2.9)
Q4	611/2,498	4.4 (3.1–6.3) **	4.5 (3.1–6.5) **	1.8 (1.1–2.8) *
Women[†]				
Q1	663/2,650	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Q2	694/2,650	1.7 (1.2–2.4) **	1.8 (1.3–2.6) **	1.3 (0.7–2.4)
Q3	648/2,650	2.3 (1.5–3.5) **	2.4 (1.5–3.8) **	1.3 (0.7–2.4)
Q4	645/2,650	5.4 (3.6–8.0) **	5.9 (4.0–8.9) **	2.0 (1.1–3.8) *

[a]*Calculated using binary logistic regression.*
[†]*Men: Q1 (uric acid ≤ 309.30 μmol/L), Q2 (309.30 < uric acid ≤ 356.90 μmol/L), Q3 (356.90 < uric acid ≤ 404.50 μmol/L), and Q4 (uric acid > 404.50 μmol/L). Women: Q1 (uric acid ≤ 232.00 μmol/L), Q2 (232.00 < uric acid ≤ 273.60 μmol/L), Q3 (273.60 < uric acid ≤ 321.20 μmol/L), and Q4 (uric acid > 321.20 μmol/L).*
Model 1 adjusted for race.
Model 2 adjusted for race, body mass index, waist circumference, drinking status, education level, hypertension, serum triglyceride, total cholesterol, and urate-lowering therapy.
*$P < 0.05$.
**$P < 0.01$.

TABLE 7 | Weighted odds ratios (95% confidence intervals) for insulin resistance, impaired fasting glucose, and hyperinsulinemia of participants with the increase of per standard deviation uric acid (Men = 2,498, women = 2,650).

	Model 2[a]
Men	
Insulin resistance	1.2 (1.0–1.5) *
Impaired fasting glucose	1.1 (0.9–1.3)
Hyperinsulinemia	1.2 (1.0–1.4) *
Women	
Insulin resistance	1.3 (1.1–1.7) **
Impaired fasting glucose	1.3 (1.1–1.6) **
Hyperinsulinemia	1.3 (1.0–1.5) *

[a]*Calculated using regression analysis.*
Model 2 adjusted for race, body mass index, waist circumference, drinking status, education level, hypertension, serum triglyceride, total cholesterol, and urate-lowering therapy.
*$P < 0.05$.
**$P < 0.01$.

TABLE 8 | Weighted odds ratios (95% confidence intervals) for insulin resistance (HOMA-IR) of participants across quartiles of serum uric acid, stratified analysis by menopause (Pre-menopausal women = 1,245; Post-menopausal women = 1,122).

	Case/Participants	Crude[a]	Model 1[a]	Model 2[a]
Pre-menopausal women[†]				
Q1	322/1,245	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Q2	354/1,245	2.2 (1.2–4.0) *	2.5 (1.4–4.7) **	2.0 (1.1–3.7) *
Q3	258/1,245	3.2 (1.8–5.7) **	3.8 (2.1–6.7) **	2.2 (1.1–4.4) *
Q4	311/1,245	8.2 (5.2–13.0) **	9.5 (6.1–14.9) **	3.5 (2.0–6.0) **
P for trend		< 0.01	< 0.01	< 0.01
Post-menopausal women[†]				
Q1	303/1,122	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Q2	285/1,122	1.1 (0.5–2.2)	1.1 (0.5–2.2)	0.6 (0.3–1.3)
Q3	257/1,122	1.7 (0.8–3.6)	1.7 (0.8–3.7)	0.9 (0.4–2.0)
Q4	277/1,122	4.1 (2.0–8.1) **	4.2 (2.1–8.6) **	1.9 (0.8–4.4)
P for trend		< 0.01	< 0.01	0.082

[a]*Calculated using binary logistic regression.*
[†]*Pre-menopausal women: Q1 (uric acid ≤ 226.00 μmol/L), Q2 (226.00 < uric acid ≤ 267.70 μmol/L), Q3 (267.70 < uric acid ≤ 303.30 μmol/L), and Q4 (uric acid > 303.30 μmol/L).*
Post-menopausal women: Q1 (uric acid ≤ 249.80 μmol/L), Q2 (249.80 < uric acid ≤ 291.50 μmol/L), Q3 (291.50 < uric acid ≤ 339.00 μmol/L), and Q4 (uric acid > 339.00 μmol/L).
Model 1 adjusted for race.
Model 2 adjusted for race, body mass index, waist circumference, drinking status, education level, hypertension, serum triglyceride, total cholesterol, and urate-lowering therapy.
*$P < 0.05$.
**$P < 0.01$.

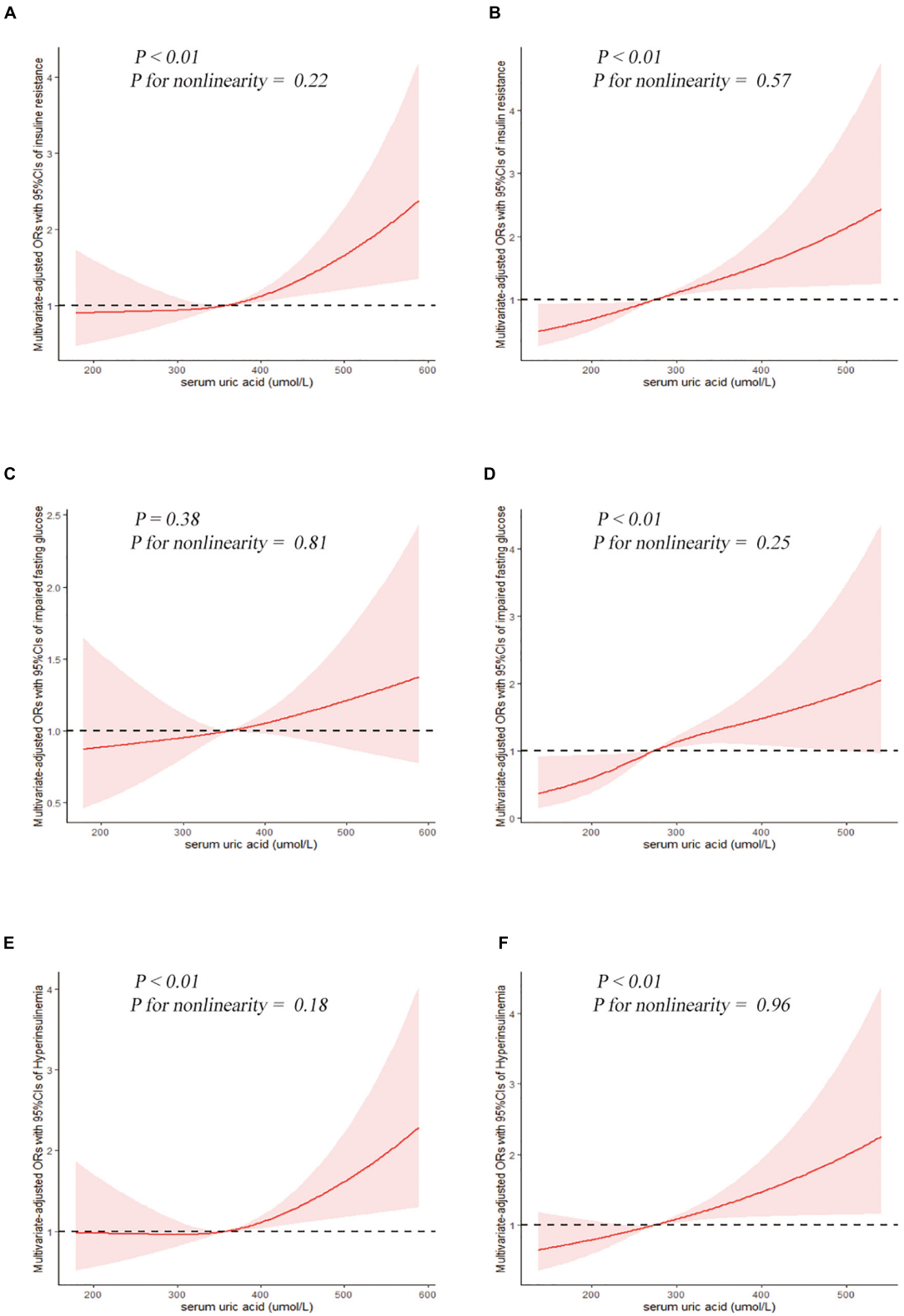

FIGURE 2 | Examination of the dose-response relationship between serum uric acid (μmol/L) and the risk of impaired glucose metabolism by restricted cubic splines model. The restricted cubic splines model adjusted for race, BMI, waist circumference, drinking status, education level, hypertension, total cholesterol, triglyceride, and urate-lowering therapy. Insulin resistance, **(A)** men and **(B)** women. Impaired fasting glucose, **(C)** men and **(D)** women. Hyperinsulinemia, **(E)** men and **(F)** women.

between SUA and the risk of hyperinsulinemia are presented in **Figures 2E,F**. Uric acid levels were positively associated with the risk of hyperinsulinemia in both men and women ($P < 0.01$, P for non-linearity = 0.18 and 0.96, respectively).

The OR values with per SD increase in SUA are presented in **Table 7**. In men, SUA was positively associated with the risk of IR and hyperinsulinemia; the ORs with per SD increase in SUA was 1.2 (1.0–1.5) and 1.2 (1.0–1.4), respectively. In women, SUA was positively associated with the risk of IR, IFG, and hyperinsulinemia; the ORs with per SD increase in SUA was 1.3 (1.1–1.7), 1.3 (1.1–1.6), and 1.3 (1.0–1.5), respectively.

The results of stratified analysis by menopausal status are presented in **Table 8**. In pre-menopausal women aged ≥20 years, the ORs with 95% CIs were 2.0 (1.1–3.7), 2.2 (1.1–4.4), and 3.5 (2.0–6.0) in Q2, Q3, and Q4, respectively, vs. Q1 of SUA in Model 2, while the ORs among different uric acid groups gradually increased (P for trend < 0.01). In the post-menopausal group, the results were significant in the crude model and Model 1 but became insignificant after full adjustment for the confounding factors.

Further sensitivity analysis was performed by excluding participants diagnosed with metabolic syndrome, finally including 4,270 participants. After full adjustment for the same confounding factors, the relationship between SUA and IR continued to be significant (**Table 9**). Compared with the lowest quartile of SUA, the OR (95% CIs) of insulin resistance in the highest quartile was 1.6 (1.1–2.3) and 1.9 (1.1–3.5) in men and women, respectively.

The results of linear regression analysis between SUA levels and HOMA-IR are presented in **Supplementary Table 1**. In men, the coefficients (β) with 95% CIs were 0.09 (−0.15 to 0.33), 0.37 (0.00–0.75), and 0.68 (0.26–1.09) in Q2, Q3, and Q4, respectively, vs. Q1 of SUA in Model 2. In women, the coefficients (β) with 95% CIs were 0.07 (−0.14 to 0.28), 0.15 (−0.15 to 0.45), and 0.41 (0.11–0.72) in Q2, Q3, and Q4, respectively, vs. Q1 of SUA in Model 2.

The results of stratified analysis based on BMI, waist circumference, drinking status, educational levels, hypertension, serum triglyceride, and total cholesterol are summarized in **Supplementary Tables 2–8**. We found that the association between SUA and IR was more pronounced among participants with obesity, bigger waist circumference, hyperlipidemia, and those with a college degree.

TABLE 9 | Weighted odds ratios (95% confidence intervals) for insulin resistance (HOMA-IR) of participants without metabolic syndrome across quartiles of serum uric acid (Men = 2,124, Women = 2,146).

		Crude[a]	Model 1[a]	Model 2[a]
Males[†]				
Q1	584/2,124	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Q2	538/2,124	1.4 (0.9–2.3) *	1.4 (0.9–2.3)	1.2 (0.7–1.9)
Q3	493/2,124	2.1 (1.4–3.1) **	2.1 (1.4–3.2) **	1.3 (0.8–2.1)
Q4	509/2,124	3.4 (2.3–4.9) **	3.4 (2.4–5.0) **	1.6 (1.1–2.3) *
Females[†]				
Q1	607/2,146	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Q2	515/2,146	1.3 (0.9–1.9)	1.4 (1.0–2.1)	1.3 (0.7–2.2)
Q3	503/2,146	2.1 (1.4–3.1) **	2.2 (1.4–3.4) **	1.7 (1.0–2.9)
Q4	521/2,146	3.4 (2.1–5.6) **	3.7 (2.2–6.1) **	1.9 (1.1–3.5) *

[a] *Calculated using binary logistic regression.*

[†] *Males: Q1 (uric acid ≤ 309.30 μmol/L), Q2 (309.30 < uric acid ≤ 350.90 μmol/L), Q3 (350.90 < uric acid ≤ 398.50 μmol/L), and Q4 (uric acid > 398.50 μmol/L). Females: Q1 (uric acid ≤ 232.00 μmol/L), Q2 (232.00 < uric acid ≤ 267.70 μmol/L), Q3 (267.70 < uric acid ≤ 309.30 μmol/L), and Q4 (uric acid > 309.30 μmol/L).*

Model 1 adjusted for race.

Model 2 adjusted for race, body mass index, waist circumference, drinking status, education level, hypertension, serum triglyceride, total cholesterol, and urate-lowering therapy.

**P < 0.05.*

***P < 0.01.*

DISCUSSION

In this study, we combined data from the NHANES 2011–2016 to investigate the relationship between SUA and impaired glucose metabolism in people without diabetes. To the best of our knowledge, this is the first study that used restricted cubic spline analysis and stratified analysis by menopausal status to investigate the above association with a large-scale sample. We found that SUA was positively correlated with IR risk in all individuals, except for post-menopausal individuals. In women, elevated UA levels were positively correlated with increased risk of IFG and hyperinsulinemia, while in men, elevated UA levels were positively correlated with increased risk of hyperinsulinemia, but not IFG. Restricted cubic spline revealed that the concentrations of SUA were positively associated with the risk of IR and hyperinsulinemia in both men and women, and the above association seemed more pronounced among women than men.

The pathophysiological mechanism for the development of IR remains unclear; however, both genetic factors and environmental factors are involved. Previous experimental studies have suggested that increasing adipose tissue can result in IR through chronic low-grade inflammation and an imbalance of pro-inflammatory and anti-inflammatory adipokines (13). While the mechanism of the relationship between SUA and IR has not yet been fully elucidated, several possible explanations have been proposed. Primarily, elevated SUA directly induces IR by increasing the production of reactive oxygen species (ROS) and inhibiting insulin receptor substrate 1 (IRS1) and protein kinase B (Akt) insulin signaling. Antioxidant N-acetyl-L-cysteine could inhibit ROS production and block hyperuricemia-induced IRS1 activation and Akt inhibition (30). In addition, uric acid could induce IR by regulating activation of the NLRP3 inflammasome. Urate-lowering therapy with allopurinol suppresses the expression of the NLRP3 inflammasome, and the knockdown of NLRP3 expression improves insulin signaling by reducing IRS1 phosphorylation and enhancing Akt phosphorylation (31). Reduction of endothelial nitric oxide supply and bioavailability, and activation of NADPH oxidase, also medicates the IR (32). On the other hand, IR is inversely correlated with the renal clearance of SUA by enhancing renal tubular reabsorption of uric acid (11, 33). Hyperinsulinemia could increase the activation of the hexose phosphate, which

promotes the biosynthesis of purine and increases the rate of uricogenesis, eventually resulting in hyperuricemia (19).

In their study, Choi et al. found that SUA levels increased linearly with HOMA-IR levels in the general United States adult population (34). A study conducted in 2020 revealed that elevated SUA was associated with a higher risk of IR in type 2 diabetes and the above association was more pronounced in female patients (18). A study conducted in 2011 found that SUA was positively correlated with IFG only in women, which was consistent with our results. The lower visceral glucocorticoid receptor density in women leads to a reduced visceral fat mass compared to that in men, and the differences in fat distribution between men and women partly explain the gender differences (35). However, in Ma's study, which only involved patients with newly diagnosed type 2 diabetes, there was no significant association between uric acid and HbA1c in the low insulin group, while an inverse relationship was found in the high insulin group (19). A study conducted by Balikcioglu et al. involving 82 obese adolescents found that uric acid was positively correlated with HOMA-IR in men but not in women (36). In another study, which involved healthy people without diabetes (n = 102), prediabetes (n = 98), and diabetes (n = 110), an inverse association was found between the SUA and fasting glucose levels and the prevalence of diabetes (37). These observations might be explained by higher renal clearance of uric acid in adult diabetic patients (38). The following reasons could potentially explain the differences in the above studies: (1) the participants involved in previous studies had different characteristics. For instance, only newly diagnosed type 2 diabetes patients were involved in Ma's study (19) and only obese adolescents in Balikcioglu's study (36). Besides, the healthy individuals and diabetic patients in Ali's study (37) came from the same university or hospital in Bangladesh, while in the present study, we only included individuals without diabetes. (2) The research methods, statistical analysis, and adjusted confounding factors differed in the above-mentioned research. Only age, BMI, blood pressure, triglyceride, and creatinine were adjusted in Ma's study (19), while branched-chain amino acid (BCAA) levels and products of BCAA catabolism were additionally adjusted in Balikcioglu's study (36). Besides, age, gender, serum lipid profile, albumin, and total protein were adjusted in Ali's study (37), while in the present study, we only additionally adjusted for race, waist circumference, drinking status, education level, and urate-lowering therapy. Analysis was also conducted separately by gender. To sum up, different participants, research methods, and the adjusted confounding factors might explain the inconsistent results.

Previous studies have reported the influence of menopausal transition on the changes in SUA. Cho et al. found that the prevalence of hyperuricemia significantly increases as the menopausal stage increases (39). Ahmed et al. suggested that a reduction of estrogen levels in post-menopausal women leads to a higher risk of type 2 diabetes mellitus (T2DM) (40). Another study found that menopause is often related to the accumulation of visceral adipose tissue (VAT), which may provoke IR and result in hyperinsulinemia (41). Also, menopausal hormone therapy may improve insulin secretion and sensitivity, thus decreasing the risk of T2DM (42). Due to the influence of menopause, we further performed a stratified analysis based on menopausal status to explore the above relationship in women without diabetes.

Our results showed that SUA was significantly associated with IR only in pre-menopausal women aged $\geq$ 20 years but not in the post-menopausal group. No previous study found this phenomenon. However, the reason for this result remained poorly understood. The sex hormone alteration in the post-menopausal period, decreasing serum estrogen and sex hormone-binding globulin, and elevated free testosterone levels could all lead to the accumulation of VAT (43, 44). As the accumulation of VAT is the main predictor of IR, we speculate that the production of pro-inflammatory factors by adipocytes and chronic low-grade inflammation state might weaken the effect of uric acid on IR in post-menopausal women. Future studies are needed to confirm the differences in the relationship between SUA and IR in women with different menopausal statuses and explore the causes of the above phenomenon.

We used a large national representative sample among the general United States population, which increased the statistical strength and confirmed the reliability of the reported results. We fully adjusted the analyses for the potential confounding factors and analyzed the association with different statistical methods. To the best of our knowledge, this is the first study that used binary logistic regression analysis to investigate the relationship between SUA and glucose metabolism, and restricted cubic splines and stratified analysis by menopausal status to explore the relationship between SUA and glucose metabolism with a large-scale nationwide sample. Due to the differences in uric acid levels between men and women, the analyses were conducted separately by gender. Therefore, it is helpful to explore the gender difference in the relationship between uric acid and impaired glucose metabolism. In the present study, we only included people without diabetes to avoid the effect of oral hypoglycemic drugs and exogenous insulin. To minimize the influence of metabolic syndrome, we performed a sensitivity analysis by excluding participants without metabolic syndrome, and the obtained results were still stable.

The present study has the following limitations: primarily, as this was a cross-sectional study, it was difficult to determine causality, so further experimental studies and large-scale prospective research are required to confirm the causality. Furthermore, the serum variables in our study were only measured once, while uric acid, fasting glucose, and insulin were not static but dynamic variables, which may be affected by the diet and cause some bias. In addition, due to the limited data, it was impossible to include all potential confounding factors. We also did not analyze the relationship between SUA and other indexes reflecting the function of islet β cells, such as the C peptide. Meanwhile, we used data from NHANES 2011 to 2016, some of which may be considered outdated, considering the changes that may have occurred due to changes in lifestyle and food habits.

With improved living conditions, the prevalence of hyperuricemia is gradually increasing. It is generally agreed that gout patients should initiate urate-lowering therapy; however, for asymptomatic hyperuricemia patients, most countries do not recommend initiating urate-lowering therapy due to the

potentially serious adverse effects. Our results suggest that more attention should be paid to the SUA level; for people with unexplained impaired glucose metabolism, screening for SUA might be necessary. For people with elevated SUA levels, even those without urate-lowering therapy, professional advice on how to control uric acid levels, such as weight loss, avoidance of alcohol, sugar-sweetened drinks, and seafood, might be helpful.

CONCLUSION

Our study suggests that SUA levels might be positively associated with impaired glucose metabolism in the general United States adult population without diabetes. We found that uric acid increased the risk of IR in pre-menopausal women aged $\geq$20 years rather than in post-menopausal women. We hope that these results can provide valuable information for the screening and treatment of impaired glucose metabolism and screening of SUA. Future studies are needed to confirm the differences in the relationship between SUA and IR in women with different menopausal statuses and explore the causes of the above phenomenon.

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 authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the National Center for Health Statistics' Research Ethics Review Board for all data collection protocols. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YH: conceptualization, resources, and writing—original draft. YC and HD: data curation. YH, XH, and HD: formal analysis. YZ and XZ: funding acquisition and writing—review and editing. YH and YY: investigation. YH and JW: methodology. YC and YH: software. YZ: supervision and validation. YH, JW, and HD: visualization. All authors helped to perform the research and read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.905085/full#supplementary-material

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Proposal for standardizing normal insulin ranges in Brazilian patients and a new classification of metabolic syndrome

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Background: Insulin resistance and/or hyperinsulinemia are closely linked to adiposity, metabolic syndrome (MetS) and prolonged inflammatory processes.

Methods: We retrospectively analyzed 1,018 adult individuals with a mean age of 46 years (74% male) and classified them as: Metabolically normal: without any of the five criteria of the International Diabetes Federation (IDF) used for the diagnosis of MetS, plus normal fasting insulin (Men $<$ 8 mU/L, Women $<$ 10 mU/L); Level 1 MetS: with one or two IDF criteria, plus hyperinsulinemia (Men: $\geq$ 8 mU/L), and Women: $\geq$ 10 mU/L); Level 2 MetS: with three or more IDF criteria, plus hyperinsulinemia.

Results: The mean values for fasting insulinemia in metabolically normal individuals was 4.6 $\pm$ 1.8 mU/L and 5.6 $\pm$ 2.3 mU/L, while their means for the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) were 1.0 and 1.2 for men and women, respectively. In addition, the mean values for insulin (and HOMA-IR) for individuals with two normal anthropometric parameters (body mass index and waist girth), or two normal anthropometric parameters plus no IDF criteria, were similar to the metabolically normal group. Based on the obtained mean + 2 SD, we established the following insulin (and HOMA-IR) values as diagnostic cut-offs for hyperinsulinemia: Men: $\geq$ 8 mU/L ($\geq$ 1.5), and Women: $\geq$ 10 mU/L ($\geq$ 2.0). The mean serum insulin was significantly higher for individuals with Level 1 MetS (approx. 9 mU/L for both genders) compared with metabolically normal individuals, as was the prevalence of hepatic steatosis, which was more evident in men. Thus, the presence of one or two abnormal IDF criteria, combined with hyperinsulinemia and/or raised HOMA-IR, suggests the presence of MetS and

insulin resistance. Patients of both genders with Level 2 MetS had higher serum insulin and/or HOMA-IR values than Level 1, as well as a higher prevalence of hypertension and hepatic steatosis, being more pronounced among men. The process was progressive and proportional to the degree of hyperinsulinemia.

Conclusion: It is proposed that intervention against MetS progression should be started in individuals with Level 1 MetS, rather than waiting for more criteria for diagnostic confirmation, which this should help to reduce the occurrence of known complications such as type 2 diabetes, atherosclerosis, hypertension, and chronic kidney disease, among others.

KEYWORDS

diabetes, HOMA-IR, insulin, hyperinsulinemia, obesity, metabolic syndrome

Background

Metabolic syndrome (MetS) is a serious disorder that results from prolonged subclinical systemic inflammation originating in adipose tissue (1–4). It is increasingly prevalent worldwide (5, 6) and threatens the continued growth of life expectancy that has been observed over the last two centuries (7).

The major factor responsible for its increased prevalence is certainly the pandemic of obesity, which is primarily caused by diets containing an excess of carbohydrates and by sedentary lifestyles (1, 8, 9). Yet, despite its recognized importance, there is no homogeneous definition of MetS. The most commonly used definitions are those of the European Group for the Study of Insulin Resistance, (10) the American Association of Clinical Endocrinologists, (11) the International Diabetes Federation (IDF), (12) and the National Cholesterol Education Program Adult Treatment Panel III 2005 (13). The first three consider insulin resistance to be a mandatory condition for diagnosis, while the latter requires the presence of three or more of the following five IDF criteria: (1) triglycerides $\geq$ 150 mg/dL; (2) high density lipoprotein-cholesterol (HDL-C) $<$ 40 mg/dL in men and $<$ 50 mg/dL in women, or patient receiving fibrate; (3) blood glucose $\geq$ 100 mg/dL; (4) increased waist girth (variable with ethnicity); and (5) hypertension $\geq$ 130 and/or/85 mm Hg, or patient receiving antihypertensive treatment (13).

Insulin resistance, hyperinsulinemia, and MetS are closely related to each other and to various medical complications such as type 2 diabetes, chronic kidney disease, hepatic steatosis, neoplasms, urinary calculosis, polycystic ovary syndrome, arthropathies, hypertension, cardiovascular diseases, and skin diseases including psoriasis (13–24).

Despite the recognized importance of MetS, the limits for diagnosing hyperinsulinemia and insulin resistance are still not clear. In this paper, we aimed to define normal values for insulin and the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index based on a Brazilian cohort, and to suggest a new and simpler classification for MetS. We propose that this will provide early recognition and promote preventive therapeutic intervention for complications.

Abbreviations: BMI, Body mass index; HDL-C, high density lipoprotein cholesterol; HS, hepatic steatosis; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; HTN, Hypertension; IDF, International Diabetes Federation; MetS, Metabolic Syndrome.

Materials and methods

Participants and study design

This was a cross-sectional, retrospective, single-center study that aimed to define the diagnostic cut-offs for fasting blood insulin and HOMA-IR in Brazilian adults of both genders. A cohort of 1,015 adult study participants (751 men, 264 women), with a mean age of 46.5 years $\pm$ 8.91, were recruited from participants who underwent elective screening consultations (check-ups) from October 2020 to March 2021. Patients were examined for comorbidities such as hypertension, diabetes, dyslipidemia, and obesity, due to their relevance to the proposed analyses.

Patient numbers varied slightly in different categories of results as some participants did not undergo a specific examination (i.e., ultrasound), and these have been noted in the text.

This study was approved by the Ethics and Research Committee of Hospital Alemão Oswaldo Cruz de São Paulo (CAAE: 46489021.6.0000.0070).

TABLE 1 Baseline characteristics of patients.

Variables	Men ($n = 751$)	Women ($n = 264$)	Total ($n = 1015$)
Age (years)	47.3 ± 9.7	44.8 ± 7.1	46.5 ± 8.9
Body Mass Index (kg/m^2)	28.2 ± 3.8	25.4 ± 4.17	27.4 ± 4.1
Waist Girth (cm)	100.6 ± 10.9	87.6 ± 10.9	96.6 ± 12.4
Systolic blood pressure (mmHg)	127.3 ± 13.5	117.9 ± 15.7	124.5 ± 14.9
Diastolic blood pressure (mmHg)	85.1 ± 9.9	75.2 ± 11.1	82.1 ± 11.3
Total Cholesterol (mg/dL)	187.8 ± 35.9	186.1 ± 36.2	187.3 ± 36.0
LDL (mg/dL)	124.0 ± 72.9	109.6 ± 32.6	119.6 ± 63.6
HDL (mg/dL)	47.7 ± 12.9	60.4 ± 15.9	51.6 ± 15.1
Triglycerides (mg/dL)	124.5 ± 70.4	92.2 ± 50.2	114.7 ± 66.5
Fasting glucose (mg/dL)	96.2 ± 13.7	91.2 ± 8.4	94.7 ± 12.5
Insulin (mU/L)	12.1 ± 8.4	9.9 ± 6.2	11.4 ± 7.8
HOMA-IR	2.9 ± 2.3	2.3 ± 1.53	2.71 ± 2.0
HbA1C (%)	5.3 ± 0.5	5.2 ± 0.5	5.28 ± 0.5
Hepatic Steatosis (n/%)	299/743 (40.2)	43/255 (16.9)	342/998 (33.7)
Serum creatinine (mg/dL)	1.8 ± 0.6	0.7 ± 0.2	1.46 ± 7.6

Clinical evaluation and sample collection for laboratory tests

Blood pressure was measured during clinical evaluations using the auscultatory method with a manual sphygmomanometer, in a seated position after at least 5 min of rest. Waist girth (cm) was measured at the midpoint between the last rib and the iliac crest. Body mass index (BMI) was calculated after confirming weight and height.

The five criteria used by the IDF for the diagnosis of MetS (13)—as listed above—were assessed, and each participant also authorized an additional blood sample and an isolated urine sample to be used for the determination of fasting serum insulin and microalbuminuria. The samples were collected after 10–12 h fasting and were analyzed in addition to the standard tests predefined by the check-up program of Hospital Alemão Oswaldo Cruz (São Paulo), at no additional cost to customers, companies, or healthcare providers.

Patients were considered normal if they had no previous diagnosis of the conditions considered criteria for MetS and which were not on regular use of drugs to treat them. Patients were diagnosed with MetS if they fulfilled the diagnostic criteria according to IDF criteria.

The standard laboratory analyses were conducted on the day of the allocated appointment, with their respective evaluation methods and reference values considered by the analysis laboratory, and included:

- Creatinine, kinetic method, colorimetric
- Blood glucose: enzymatic method

TABLE 2 Anthropometric parameters of BMI and Waist Girth compared to insulin and HOMA-IR in men and women.

BMI ranges	n (%)	Insulin (mU/L) mean ± SD	HOMA-IR mean ± SD
Men			
17.8–22.9	51 (6.7%)	5.80 ± 2.88^{a**}	1.34 ± 0.69^{b**}
23–24.9	121 (16.1%)	7.52 ± 4.91^{a**}	1.77 ± 1.18 ^{b**}
25–29.9	374 (49.6%)	10.4 ± 5.58 ^{a**}	2.46 ± 1.40 ^{b**}
≥ 30	207 (27.5%)	17.2 ± 14.3 ^{a**}	4.26 ± 3.92 ^{b**}
Women			
17.8–22.9	91 (34.3%)	6.35 ± 2.50^{c**}	1.38 ± 0.60^{d*}
23–24.9	45 (17%)	7.93 ± 3.17^{c**}	1.76 ± 0.69^{d*}
25–29.9	88 (33.2%)	10.6 ± 5.83^{c**}	2.46 ± 1.48^{d*}
≥ 30	41 (15.4%)	15.4 ± 7.23^{c**}	3.73 ± 2.02^{d*}
Waist ranges (cm)	**n (%)**	**Insulin (mU/L) mean ± SD**	**HOMA-IR mean ± SD**
Men			
< 90	106 (14.1%)	6.30 ± 4.00^{e**}	1.47 ± 0.98^{f*}
90–99.9	266 (35.4%)	9.43 ± 5.53^{e**}	2.21 ± 1.35^{f*}
≥ 100	380 (50.5%)	14.4 ± 11.5^{e**}	3.52 ± 3.14^{f*}
Women			
< 80	64 (24%)	6.05 ± 2.58^{g**}	1.31 ± 0.58^{h**}
80–89.9	98 (37%)	7.87 ± 3.30^{g**}	1.76 ± 0.83^{h**}
≥ 90	102 (38.6%)	13.0 ± 6.89^{g**}	3.08 ± 1.83^{h**}

a-h: comparison among groups according to the respective letter. For BMI (753 men, 265 women, 1,018 total), insulin and HOMA-IR means were significantly different by $^{*}p < 0.05$ or $^{**}p < 0.005$; for waist girth (752 men; 264 women; waist not recorded for 1 man and 1 woman; 1,016 total), means differed by $^{*}p < 0.05$ or $^{**}p < 0.001$.

- Fasting insulin: electro chemiluminometric assay
- HOMA-IR (Homeostatic Model Assessment for Insulin Resistance
- HDL-C (high density lipoprotein cholesterol): homogeneous enzyme assay
- Triglycerides: enzymatic assay
- Microalbumin in an isolated urine sample: by immunoturbidimetry (mg/g creatinine).

In addition, hepatic steatosis was assessed using abdominal ultrasound by the same team and equipment.

Statistical analysis

The D'Agostino-Pearson omnibus and Shapiro–Wilk tests were used to assess the distribution of variables. Variables with parametric distribution were expressed as mean ± standard deviation and compared using the Student's *t*-test when in two groups and using analysis of variance (ANOVA) when in three or more groups. Where data distributions were non-parametric, the variables were expressed as median and interquartile ranges, and compared using the Mann–Whitney

TABLE 3 Insulin and HOMA-IR values of participants with: (A) normal anthropometric parameters (BMI and Waist); (B) no IDF criteria; or (C) normal anthropometric parameters (BMI and Waist) and no IDF criteria.

Gender		Insulin (mU/L)				HOMA-IR			
	n (%)	Mean	SD	Mean + 1 SD	Mean + 2 SD	Mean	SD	Mean + 1 SD	Mean + 2 SD
(A)									
Men	18 (2.4%)	4.3[a]*	1.4	5.7	7.1	1.0[d]*	0.35	1.35	1.70
Women	38 (14%)	5.4[a]*	2.3	7.7	10	1.2[d]*	0.5	1.7	2.20
(B)									
Men	49 (6.5%)	4.6[b]*	1.8	6.4	8.2	1.0[e]*	0.4	1.4	1.8
Women	48 (18%)	5.6[b]*	2.3	7.9	10.2	1.2[e]*	0.5	1.7	2.2
(C)									
Men	11(1.5%)	4.0[c]*	1.6	5.6	7.2	0.9[f]*	0.3	1.2	1.5
Women	33(4.4%)	5.3[c]*	2.2	7.5	9.7	1.1[f]*	0.5	1.6	2.1

Normal anthropometric ranges were defined as: BMI < 23; Waist < 90 (men), < 80 (women); a-f: comparison among groups according to the respective letter. *Insulinemia and HOMA-IR means were statistically different between men and women ($p < 0.005$). $n = 752$ men (1 man excluded as insulin not recorded); 265 women; 1,017 total.

U test for two groups or the Kruskal–Wallis test among three or more groups. Nominal variables were expressed as absolute and percentage counts and were analyzed using the Chi-squared or Fisher's exact test. We used the analysis of Receiver Operator Characteristics (ROC) curves to evaluate the accuracy of insulin and HOMA-IR values for the prediction of metabolic syndrome for male and female patients. Values of $p < 0.05$ or, in the case of multiple comparisons, q less than 0.05 were considered statistically significant. Statistical analyses were performed using GraphPad Prism version 8.00 (GraphPad Software, San Diego, CA, United States) and SPSS 25.0 (IBM Corp, Armonk, NY, United States) software programs.

Results

The cohort of 1,015 adult study participants (751 men, 264 women) had a mean age of 46.5 ± 8.9 years old. The baseline characteristics of patients are described on Table 1. The relationship between ranges of two anthropometric parameters (BMI, Waist girth) compared with insulin and HOMA-IR are described on Table 2.

The lowest ranges of these two anthropometric parameters were used to define normal insulin and HOMA-IR values: BMI < 23 for men and women; Waist < 90 cm and < 80 cm for men and women, respectively. These anthropometric normal ranges were then combined in an analysis with the five IDF criteria for MetS (Table 2).

Based on the mean + 2 SD values for insulin and HOMA-IR observed in Table 3, as well as a ROC curve co-ordinates, we defined the following diagnostic cut-offs for hyperinsulinemia (and raised HOMA-IR): Men ≥ 8 mU/L (sensitivity: 82.4% and specificity: 58%) and HOMA-IR ≥ 1.5 (sensitivity: 91.3% and specificity: 51%) and Women ≥ 10 mU/L (sensitivity: 78.6% and specificity: 72.5%) and HOMA-IR ≥ 2.0 (sensitivity: 83.9% and specificity: 70.2%).

Based on those data, a new classification for diagnosis of MetS is proposed:

- Metabolically normal: fasting insulinemia Men < 8 mU/L, Women < 10 mU/L, and no IDF criteria for the diagnosis of MetS.
- Level 1 MetS: hyperinsulinemia, plus one or two IDF criteria for the diagnosis of MetS.
- Level 2 MetS: hyperinsulinemia, plus three or more IDF criteria for the diagnosis of MetS.

The proportion of metabolically normal and MetS patients (Level 1 and Level 2) according to insulinemia below and above the established cut-off may be observed in Figure 1. The statistical differences for the men with insulinemia ≥ 8 mU/L were highly significant ($p < 0.001$) between normal, Level 1 MetS, and Level 2 MetS. These highly significant trends were repeated for women with insulin ≥ 10 mU/L.

The participants were then conveniently subdivided into insulin ranges from 2–4, 5–7, 8–10, 11–15 and ≥ 16 mU/L (Figure 2). This showed a lower percentage of normal individuals and a higher percentage of patients with MetS in parallel with the increase in serum insulin values.

According to our definition (Table 4), metabolically normal individuals are normotensive. The mean insulin concentrations found in both male and female participants with Level 1 MetS and Level 2 MetS were significantly higher than the insulin means of metabolically normal patients. The mean insulin of Level 2 MetS patients was also statistically higher to that of Level 1 MetS (e.g., the higher the MetS level of MetS, the higher the insulin values in men and women). These highly significant differences were also reflected in the HOMA-IR values.

Similar trends for insulin and HOMA-IR were also observed for the proportions of hepatic steatosis (HS) in both men and women. However, 10% of men with two normal anthropometric parameters (and 4% of men with

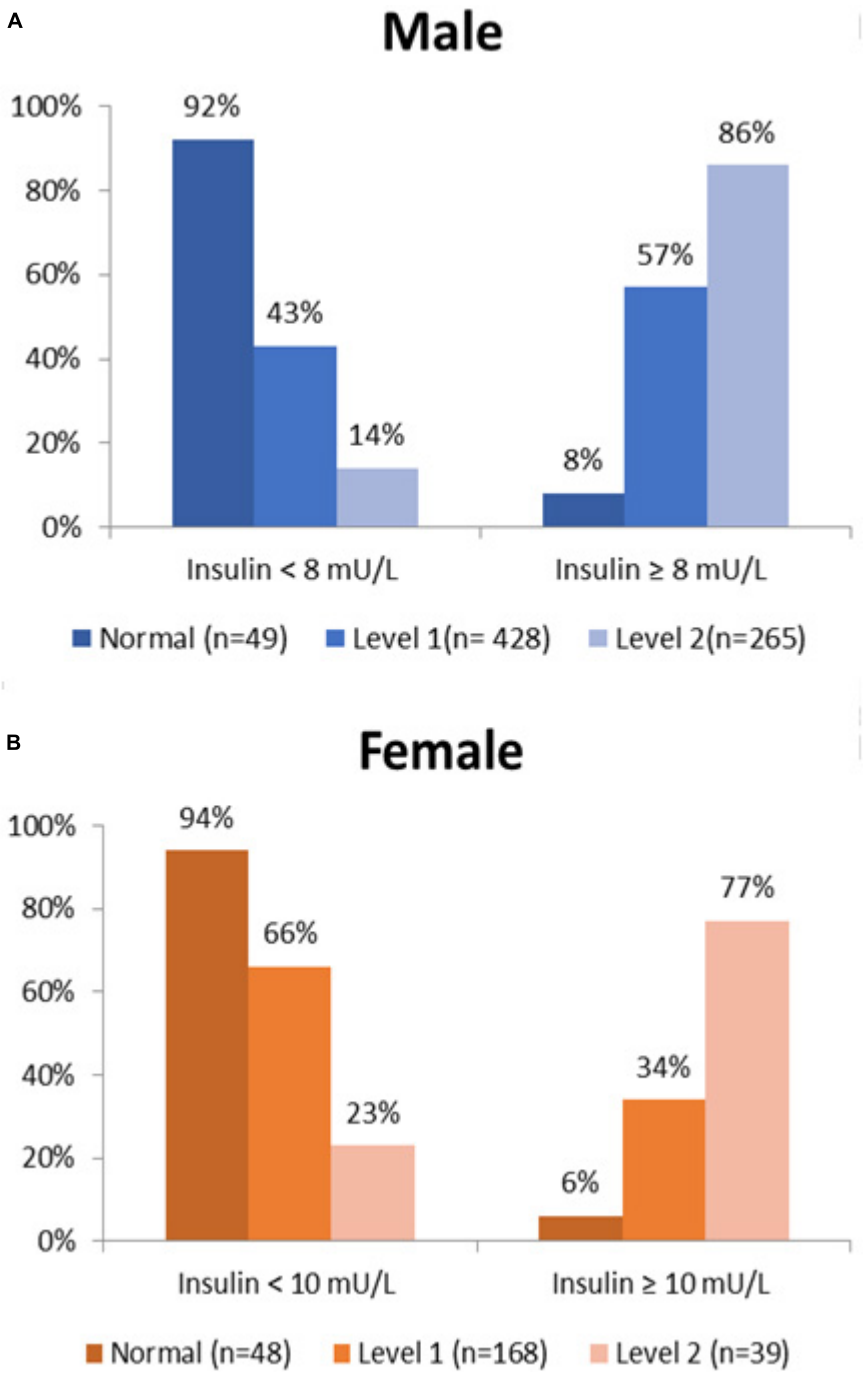

FIGURE 1
Proportion of normal and MetS patients vs. insulin cut-offs for **(A)** men and **(B)** women.

no IDF criteria) were found to have hepatic steatosis, possibly related to alcohol intake or another cause. The proportion of patients with hypertension was significantly greater among men with Level 2 MetS compared to men with Level 1 MetS, and this trend was also observed among the women.

As metabolic syndrome may progress to renal failure and albuminuria, renal function was also assessed in the patient cohort by serum creatinine and microalbuminuria. However, no significant differences were found between the normal and MetS groups. This may have been the result of the late evolution of renal complications.

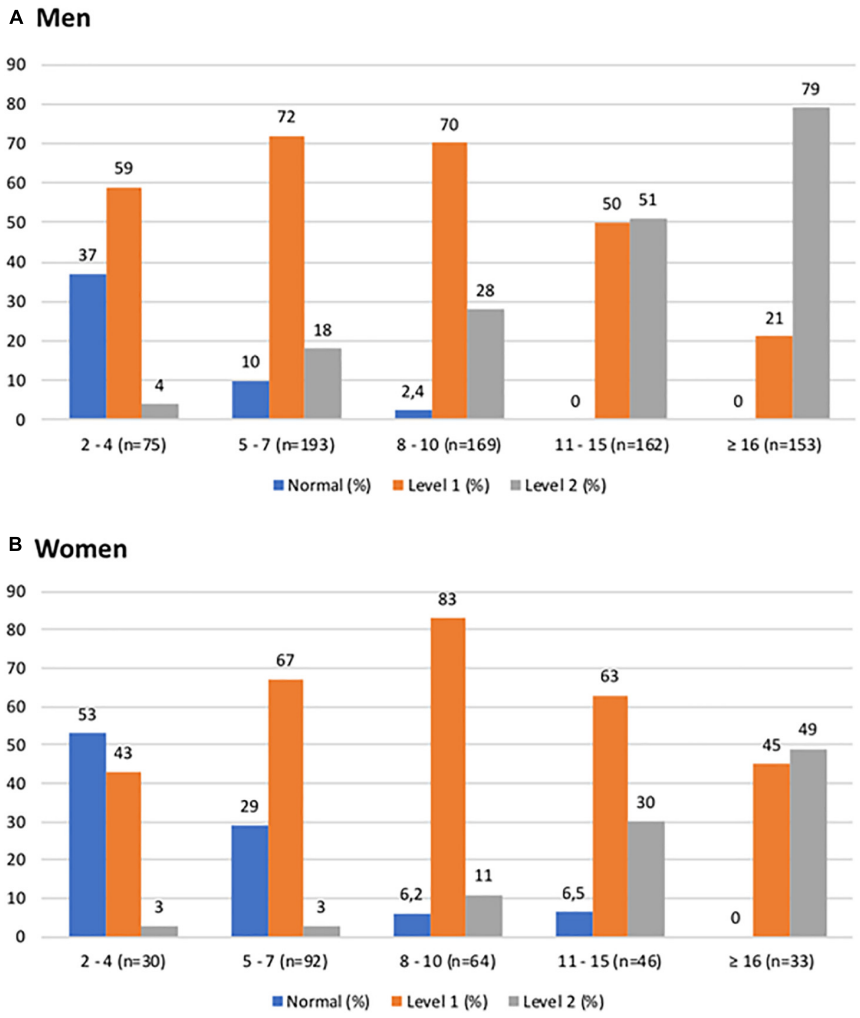

FIGURE 2
Proportion of patients classified as normal, Level 1 MetS, or Level 2 MetS, vs. ranges of fasting insulin (mU/L) for **(A)** men and **(B)** women.

Discussion

The prevalence of metabolic syndrome (MetS) varies between countries and between regions of the same country. In a study conducted in a city in the southern region of Brazil (Paraná State), MetS was confirmed in approximately 50% of the adult population over 40 years of age and in both genders (25). In another study carried out in the city of Niterói (Southeast Region, Brazil), a prevalence of about 60% was observed in older adults, based on the criteria defined by the IDF (26).

MetS is a set of clinical abnormalities which include obesity, hypertension, dyslipidemia, hyperglycemia, and hyperinsulinemia. It is associated with a prolonged subclinical inflammatory process evidenced by a series of biomarkers such as pro-inflammatory cytokines, pro-oxidants, and prothrombotic factors (1, 4, 27–31).

Hyperinsulinemia has long been considered secondary to insulin resistance resulting from an inflammatory process generated by adiposity. However, it has more recently been found to be directly responsible for the inflammatory condition and for obesity (32–37). Insulin has a double action in the endothelium. It normally plays a protective role by increasing the production of nitric oxide, which is an important vasodilator and anti-aggregant that limits the growth of muscle cells. Insulin can also interfere with the release of endothelin ET-1, which is a potent vasoconstrictor. However, the beneficial effects of insulin that predominate under normal conditions are reversed in the face of insulin resistance and hyperinsulinemia (29).

Hyperinsulinemia increases the apoptosis of endothelial progenitor cells that are important for the maintenance of endothelial function and that may promote both muscle cell proliferation and atherogenesis (29, 30, 38, 39). It can also cause a specific form of cardiomyopathy, which is characterized by

TABLE 4 Insulin and HOMA-IR parameters in normal, Level 1 MetS, or Level 2 MetS patients, and% hepatic steatosis (HS) and hypertension (HTN) in each group.

Gender	n	Insulin (mU/L) mean ± SD (range)	HOMA-IR mean ± SD (range)	HS (%)	HTN (BP ≥ 130/85) (%)
Men					
Normal	49	4.6 ± 1.8 (2–10)	1.01 ± 0.43 (0.4–2.4)	4	0
Level 1 MetS	428	9.3 ± 5.5[a]* (2–48)	2.1 ± 1.33[c]* (0.4–11.6)	31	40
Level 2 MetS	265	15.6 ± 9.0[a]* (2–60)	3.9 ± 2.47[c]* (0.9–18)	60	83
Women					
Normal	48	5.6 ± 2.3 (2–13)	1.20 ± 0.50 (0.4–3)	0	0
Level 1 MetS	168	9.1 ± 4.9[b]* (3–34)	2.00 ± 1.65[d]* (1.6–7.9)	13	21
Level 2 MetS	39	15.4 ± 7.1[b]* (5–31)	3.9 ± 2.03[d]* (1.1–7.9)	49	78

HS, Hepatic Steatosis; HTN, Hypertension; a-d: comparison among groups according to the respective letter; 752 men (1 patient's insulin was not measured); 265 women; 1,017 total. *Significantly different to normal—the effects were large, so p values were < 0.001.

diastolic dysfunction, fibrosis, and heart failure, regardless of hypertension and atherosclerosis. This is secondary to abnormal coronary microcirculation, and activation of the sympathetic nervous and renin-angiotensin-aldosterone systems (17). It should be noted that hyperinsulinemia is a risk factor regardless of whether the patient is thin or obese, (40) diabetic or not (41).

The presence of hyperinsulinemia is clearly responsible for MetS damage, yet despite this importance, the reference points for insulin levels are variable and often incorrect. Some clinical analysis laboratories have established normal insulin limits up to 25 mU/L, or more. Other authors (37, 42) have defined fasting hyperinsulinemia as insulin levels of above 12 mU/L, while still others have suggested limits below 10 mU/L (43). Hyperinsulinemia has also been defined as the 75th percentile of the sum of the distribution in the normotensive, non-obese group, with normal glycemia (44).

The cut-offs obtained for the diagnosis of hyperinsulinemia (and raised HOMA-IR) in the present study [i.e., Men ≥ 8 mU/L (≥ 1.5), Women ≥ 10 mU/L (≥ 2.0)], are lower than those considered as the reference points by most clinical analysis laboratories. As can be observed, only 8% of men and 6% of women with insulin above the cut-offs defined for the diagnosis of hyperinsulinemia were considered metabolically normal in our cohort.

The proportion of participants considered metabolically normal significantly decreased with insulin values above the cut-offs and increased in participants with Level 1 or Level 2 MetS. This distribution clearly differentiated between the groups, validating the cut-off defined for the diagnosis of hyperinsulinemia, and consolidating the importance of the metabolic classes proposed in this analysis (normal, Level 1, and Level 2 MetS). These data were even more evident in **Figure 2**, which expanded the hyperinsulinemia ranges.

The various criteria used for diagnosis of MetS and its associated complications certainly do not appear concurrently. Instead, they appear over time and are preceded by prolonged exposure to hyperinsulinemia, which can be an earlier marker of metabolic risk (21–24, 30, 31, 43, 45–49).

A clear definition of the diagnostic cut-off for hyperinsulinemia will allow for early prevention and therapeutic intervention, before the emergence of the recognized and multiple morbidities associated with MetS, such as type 2 diabetes, cardiovascular diseases, and neoplasms. Our proposal to classify individuals as metabolically normal, Level 1 MetS, or Level 2 MetS is aimed at recognizing the clinical importance of hyperinsulinemia and the early stages of the syndrome, regardless of the number of IDF criteria exhibited by a patient.

Insulin values were significantly higher in patients with Level 1 MetS than in those considered metabolically normal (i.e., without any of the five IDF criteria defined previously), as was the prevalence of steatosis and hypertension. This showed that the presence of one or two of the IDF criteria already suggests the presence of insulin resistance and metabolic dysfunction. Without effective medical intervention, these individuals will likely develop MetS to its fullest extent over time, as evidenced by participants with Level 2 MetS who had even greater hyperinsulinemia and/or HOMA-IR values, and a higher prevalence of HTN and HS, compared to patients with Level 1 MetS. No significant changes in renal function, as assessed by the means for serum creatinine or microalbuminuria, were detected between the normal vs. the MetS groups, probably because these are late complications.

Our study has some limitations. First, it is a retrospective study with data from Brazilian patients who underwent annual check-up exams, which makes the study findings valid only for Brazil. However, such design of study can serve as a model for other countries and, perhaps, contribute to standardization of insulin reference levels at a global level. In addition, there is no information about the dietary and physical activity patterns of these individuals what may contribute to the MetS.

In summary, studies to evaluate the benefits of an early approach of patients with fasting insulin values above normal cut-offs, i.e., 8 mU/L in men and 10 mU/L in women (and/or HOMA-IR upper limits of 1.5 and 2.0), despite the number of diagnostic criteria for MetS (Level 1 MetS) to reduce cardiovascular events are necessary.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

This study was approved by the ethics and research committee of Hospital Alemão Oswaldo Cruz de São Paulo (CAAE: 46489021.6.0000.0070). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

PC: conception and design, data acquisition, analysis and interpretation, drafting the article, critically revising the article, funding acquisition, and supervision of the research group. JD: data interpretation, drafting the article, and critically revising the article. VS, PM, and AC-N: data analysis and interpretation, drafting the article, and critically revising the article. SM, ÉO, LP, AB, and FS: data analysis and interpretation and critically revising the article. All authors have read and approved the final version of the manuscript.

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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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Activities of daily living and its influencing factors for older people with type 2 diabetes mellitus in urban communities of Fuzhou, China

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Background: Type 2 diabetes mellitus (T2DM) is an independent risk factor for functional limitations among the older population. The predicted increase in T2DM cases combined with the ongoing rapidly aging population may further burden the already overloaded healthcare system and aggravate the loss of economic self-sufficiency. This study aimed to investigate the activities of daily living (ADL) and its influencing factors on older people with T2DM, and to provide implications for the development and improvement of community nursing services in the context rapidly aging population in China.

Methods: From March 2019 to June 2020, we conducted a cross-sectional questionnaire survey among older T2DM patients in Fuzhou, using a multi-stage cluster sampling approach. Functional status was measured by the Lawton ADL scale. Stata "nptrend" test was used to examine the trend of ordinal variables on ADL. Non-conditional logistic regression was used to identify factors affecting ADL limitations.

Results: A total of 2016 questionnaires were received, with a response rate of 96%. 12.4% of participants suffered from varying degrees of functional impairment. ADL limitations increased with age. More comorbidities were associated with a greater risk of developing functional limitations in ADLs. the following sub-groups were more likely to suffer from ADL impairment: those aged 70 and over years (OR = 1.99, 95%CI 1.77–2.56), living in an aged care house or with spouse/children (OR = 2.31, 95%CI 1.25–4.26), low monthly income (OR = 1.49, 95%CI 1.28–1.64), without health insurance (OR = 1.82, 95%CI 1.40–2.40), tight family expenses (OR = 1.95, 95%CI 1.42–2.69), having stroke (OR = 6.70, 95%CI 2.22–20.23) or malignant tumor (OR = 4.45, 95%CI 1.27–15.53), irregular eating habit (OR = 2.55, 95%CI 2.23–2.92), smoking (OR = 1.40, 95%CI 1.22–1.60), sedentary lifestyle (OR = 2.04, 95%CI 1.46–2.85), lack of physical exercise (OR = 1.35, 95%CI 1.19–1.53), sleeping difficulty (OR = 1.25, 95%CI 1.10–1.42), and lack of family support (OR = 1.19, 95%CI 1.10–1.29).

Conclusion: Older adults (≥70 years) with T2DM had a high prevalence of functional limitations across a range of daily living tasks, which not only affect individual life of quality but also present a huge burden on the family, health services system, and the whole society. Identified factors associated with ADL limitations may provide useful information for targeted nursing practice and health promotion.

KEYWORDS

type 2 diabetes, ADL, elderly, functional limitation, comorbidities, Fuzhou

Introduction

Type 2 diabetes mellitus (T2DM) is a serious public health concern. According to the latest 10th Edition IDF (International Diabetes Federation) Report (1), about 537 million people were living with diabetes (over 90% being T2DM) worldwide in 2021 and ∼6.7 million people have died from it or its complications at the same year. Driven by a complex interplay of multifarious factors such as the rapidly aging population, increased sedentary lifestyle, and abrupt changes in traditional dietary habits (2), T2DM has become one of the fastest-growing global health emergencies in this century, with the projected prevalence rate reaching 7,079 individuals per 100,000 by 2030 (3). China has the largest numbers of both current (accounting for about one-quarter of global cases) and projected T2DM cases partly due to its large population size (1). From 1990 to 2016, the all-age morbidity and mortality rates in China have dramatically increased by 78.4 and 63.5% (4), respectively, presenting huge healthcare and economic burden on the society.

T2DM is a prevalent chronic health condition more frequently affecting people aged 65 and over. Results of the 2017 national epidemiological survey showed that the prevalence of diabetes was 30.2% in people aged ≥60 years and the pre-diabetes prevalence rate reached 47.7%, although the proportion of undiagnosed cases was estimated to be 51.7% (1). Older T2DM patients were found to have an accelerated decline in leg lean mass, muscle strength and functional capacity when compared with normoglycemic control groups (5). Evidence has shown that T2DM is an independent risk factor for functional limitations among the older population (6), impairing about 60% of activities of daily living (ADL) for diabetic people aged>65 years compared with only 34% for the same age group without T2DM in the USA (7), especially among older Mexican Americans with T2DM (8). Moreover, T2DM patients were two to three times more likely to suffer from disability than their counterparts (9), and utilized healthcare services more frequently as well. Therefore, the predicted increase in T2DM cases combined with the ongoing rapidly aging population may further burden the already overloaded healthcare system and aggravate the loss of economic self-sufficiency.

Effective diabetes self-management is critical for maintaining health and preventing the occurrence of further diabetes-related complications such as diabetic ketoacidosis, hypoglycemia, cardiovascular diseases, retinopathy, nephropathy, vascular nephropathy, and foot complications (6). However, self-management can be especially challenging for elderly people with T2DM, as they are more likely to suffer from functional limitations and develop geriatric syndromes than those without diabetes (8, 9). Results of a survey including 1,691 individuals sampled from 5 provinces of China showed that T2DM patients especially those living in a low socioeconomic status were moderately satisfied with urban community health services (10), indicating room to improve diabetes caring services at a community level in the aspects of healthcare services quality, health promotion, health insurance, and the essential drug system (10, 11). Currently, few studies in China have investigated the extent to which older adults suffer from functional limitations due to T2DM and its related complications. This study aims to investigate older T2DM patients' activities of daily living (ADL) and identify its influencing factors. Findings of this study can provide useful evidence for the provision of targeted community healthcare services for older people with T2DM to improve their quality of life.

Materials and methods

Study design and participant recruitment

Located on the southeast coast of China, Fuzhou is the capital city of Fujian Province, with a population of around 8 million in 2020. In line with the national trend, Fuzhou has stepped into an aging society since 2000 (12). The aging of Fuzhou's population is still ongoing at a rapid pace, and the proportion of people aged >60 years increased from 12.1% in 2011 to 19.1% in 2020 (13). In terms of T2DM, the age-standardized prevalence rate (12.3%) of T2DM in Fuzhou was slightly higher than the national average level (11.2%) in 2017 and similarly for the age-standardized mortality rate

(14.7 per 100,000 vs. 12.7 per 100,000) (14–16). Since 2009, Chinese government launched the National Basic Public Health Service Program (NBPHSP) to provide 14 categories of health services to all urban and rural residents free of charge. NBPHSP covers the management of T2DM patients, including screening, regular follow-up, and health education (17). Local community health service centers and village clinics are responsible for the provision of NBPHSP services.

From March 2019 to June 2020, we conducted a cross-sectional questionnaire survey among T2DM patients in Fuzhou to investigate their ADLs. T2DM patients were approached under the support of local community health service centers when they carried out the NBPHSP services for T2DM patients. In this study, T2DM patients were recruited through a multi-stage random cluster sampling process. Firstly, two of the five urban districts in Fuzhou were randomly selected through drawing lots (Names of the five districts were put into a bowl and two names were randomly chosen). The two sampled districts (Taijiang District and Gulou District) have 22 community health service centers; Secondly, we assigned a unique number from 1 to 22 to each of the 22 community health service centers. Then, 11 of the 22 community health service centers were randomly selected as our study sites through an online random number generator (https://epitools.ausvet.com.au/randomnumbers). The inclusion criteria were T2DM patients aged ≥60 years. Those could not answer the survey questions because of health issues (e.g., dementia or/and mental disorders) were excluded. Participation was completely voluntary and no incentives were offered. Informed consent was obtained from individual participants. The study has been approved by the Medical Ethics Committee of Fujian Health College.

Questionnaire design

The questionnaire consists of two parts. The first section requested the following demographic information: age, gender, education level, marital status, household income, comorbidities, family support, and individual living habits (e.g., smoking, drinking, sleeping, physical exercise, eating pattern). The second section is the widely used Lawton ADL scale (validated Chinese version) to measure two important domains of functioning of older people with T2DM: physical self-maintenance scale (PSMS) and instrumental activities of daily living (IADL) (18). PSMS contains ratings of self-care ability necessary for living in the community in areas of toileting, feeding, dressing, bathing, and locomotion. In contrast, IADL contains a more complex set of behaviors required for independent living skills, including the following eight areas: telephoning, shopping, food preparation, housekeeping, laundering, use of transportation, use of medicine, and financial behavior. Each item of PSMS and IADL was measured using a 4-point Likert scale question: "do it completely by yourself," "a little difficult to do it independently," "do it with assistance," and "must be done by others." They were assigned 1–4 scores, respectively. Therefore, PSMS has a summary score from 4 to 24 and

TABLE 1 Functional limitation in older people with type 2 diabetes in Fuzhou City.

Dimension	Item	Normal *n* (%)	Impaired *n* (%)	Impaired rate *n* (%)
PSMS (scores) 6.20 ± 1.10	Dressing	1976 (98.0)	40 (2.0)	104 (5.2)
	Grooming	1977 (98.1)	39 (1.9)	
	Feeding	1980 (98.2)	36 (1.8)	
	Physical ambulation	1942 (96.3)	74 (3.7)	
	Toilet	1953 (96.9)	63 (3.1)	
	Bathing	1942 (96.3)	74 (3.7)	
IADL (scores) 8.71 ± 2.49	Ability to use telephone	1935 (96.0)	81 (4.0)	242 (12.0)
	Shopping	1869 (92.7)	147 (7.3)	
	Food preparation	1869 (92.7)	147 (7.3)	
	Housekeeping	1839 (91.2)	177 (8.8)	
	Laundry	1838 (91.2)	178 (8.8)	
	Mode of transporation	1899 (94.2)	117 (5.8)	
	Responsibility for own medications	1921 (95.3)	95 (4.7)	
	Ability to handle finances	1907 (94.6)	109 (5.4)	
ADL (scores) 14.91 ± 3.38	1766 (87.6)	250 (12.4)		

PSMS refers to "physical self-maintenance scale," IADL refers to "instrumental activities of daily living," and ADL refers to "activities of daily living". The scores of PSMS, IADL, and ADL were summarized as mean ± standard deviation; and ADL, PSMS and IADL were defined as "impaired" if the summary scores exceeded 14, 6, and 8, respectively.

IADL has a summary score from 8 to 32. The higher the score means the greater the person's functional limitation. ADL consists of PSMS and IADL, with a summary score from 14 to 56. The severity of ADL was classified into three levels: normal (14 scores), somewhat impaired (15–21 scores), and severely impaired (≥22 scores). PSMS and IADL were defined as "impaired" if the summary scores exceeded 6 and 8, respectively.

After a pilot survey, the questionnaire was revised to ensure all questions were clear and understandable. The questionnaire has also been reviewed by relevant experts. All investigators received unified training to ensure the survey was carried out consistently. Participants filled out the questionnaire by themselves under the support/assistance of an on-site investigator in the local community health service center. Completed questionnaires were checked and collected by the investigators on the spot.

Statistical analysis

Data entry was facilitated using EpiData 3.1 software (EpiData Association, Odense M, Denmark). The demographic characteristics of ADL were descriptively analyzed. The scores of functional impairments were summarized as mean ± standard deviation. Kruskal-Wallis H test and Mann-Whitney *U* test were conducted as the first step to identifying factors associated with ADL. Stata "nptrend" test was used to examine the trend of ordinal variables on ADL (19). Then, we put statistically significant factors into a non-conditional logistic regression model to identify the factors influencing ADL (inclusion criterion $\alpha = 0.05$, elimination criterion $\alpha = 0.10$). Stata 16.0 was used to perform all statistical analyses. Results were considered statistically significant at a $P < 0.05$.

TABLE 2 Comparison of activities of daily living (ADL) by demographic characteristics in older people with type 2 diabetes.

Item	*n*	ADL			*H* /*Z*	*P*-value
		Normal	Somewhat impaired	Severely impaired		
Age (years)*					52.13	<0.001
60–69	902	824 (91.4)	67 (7.4)	11 (1.2)		
70–79	835	731 (87.6)	62 (7.4)	42 (5.0)		
≥80	279	211 (75.6)	36 (12.9)	32 (11.5)		
Gender					−2.53	0.01
Male	910	779 (85.6)	82 (9.0)	49 (5.4)		
Female	1,106	987 (89.2)	83 (7.5)	36 (3.3)		
Marital status					−4.19	<0.001
Married	1,779	1,578 (88.7)	136 (7.6)	65 (3.7)		
Alone	237	188 (79.3)	29 (12.2)	20 (8.5)		
Education level*					1.19	0.88
Illiteracy	155	134 (86.4)	15 (9.7)	6 (3.9)		
Primary school	422	364 (86.3)	41 (9.7)	17 (4.0)		
Junior high school	648	569 (87.8)	50 (7.7)	29 (4.5)		
Senior high/technical school	550	486 (88.4)	40 (7.3)	24 (4.3)		
College and above	241	213 (88.4)	19 (7.9)	9 (3.7)		
Monthly income (Yuan)*					68.31	<0.001
<1,000	207	163 (78.7)	24 (11.6)	20 (9.7)		
1,000–1,999	244	181 (74.2)	51 (20.9)	12 (4.9)		
≥2,000	1,565	1,422 (90.9)	90 (5.7)	53 (3.4)		
Health insurance*					14.41	<0.001
Completely covered	256	240 (93.8)	10 (3.9)	6 (2.3)		
Partially covered	1,724	1,499 (86.9)	148 (8.6)	77 (4.5)		
Not covered	36	27 (75.0)	7 (19.4)	2 (5.6)		
Total	2,016	1,766 (100.0)	165 (100.0)	85 (100.0)		

*Refers to Kruskal-Wallis H test; otherwise, it is Mann-Whitney U test; H/Z is the statistical parameter of Kruskal-Wallis H test and Mann-Whitney U test, respectively; The severity of ADL was classified into three levels: normal (14 scores), somewhat impaired (15–21 scores), and severely impaired (≥22 scores).

Results

A total of 2,016 questionnaires were received, with a response rate of 96%, including 995 participants recruited from Taijiang District and 1,021 participants from the Gulou District. As shown in Table 1, the average ADL self-care ability score was 14.91 ± 3.38 points. 12.4% of participants suffered from varying degrees of functional impairment, of which 8.2% were mild and 4.2% were severe. The average points for PSMS and IADL were 6.20 ± 1.10 and 8.71 ± 2.49, respectively. Accordingly, the percentages of participants with impaired function for PSMS and IADL were 5.2 and 12.0%, respectively.

Differences in the functional capability of participants with T2DM by demographic characteristics are summarized in Table 2. We found ADL functions were significantly affected by the following demographic factors: age ($H = 52.13$, $P < 0.01$), gender ($Z = -2.53$, $P = 0.01$), marital status ($Z = -4.19$, $P < 0.01$), monthly income ($H = 68.31$, $P < 0.01$), and health insurance status ($H = 14.41$, $P < 0.01$). Moreover, with the increase in age ADL functions demonstrated a decreasing trend ($Z = 12.06$, $P < 0.001$). Conversely, education level ($Z = -2.4$, $P = 0.017$) and financial status ($Z = -3.99$, $P < 0.001$) showed an increasing trend with ADL functions.

Table 3 summarizes the differences in ADL functions by individual behaviors. We found the following factors

TABLE 3 Comparison of activities of daily living (ADL) functions by individual behaviors in older people with type 2 diabetes in Fuzhou.

Variable	*n*	ADL			*H* /*Z*	*P*-value
		Normal (*n* = 1,766)	Somewhat impaired (*n* = 165)	Severely impaired (*n* = 85)		
Eating habit*						
Very regular	1,257	1,183 (94.1)	47 (3.7)	27 (2.2)	138.92	<0.001
Regular	653	511 (78.2)	99 (15.2)	43 (6.6)		
Irregular	106	72 (67.9)	19 (17.9)	15 (14.2)		
Smoking*					14.88	<0.001
Yes	171	137 (80.1)	26 (15.2)	8 (4.7)		
No	1,742	1,546 (88.8)	126 (7.2)	70 (4.0)		
Ex-smoker	103	83 (80.6)	13 (12.6)	7 (6.8)		
Drinking					−3.28	<0.001
Yes	117	91 (77.8)	18 (15.4)	8 (6.8)		
No	1,899	1,675 (88.2)	147 (7.7)	77 (4.1)		
Doing exercise*					32.82	<0.001
Frequently	854	779 (91.2)	59 (6.9)	16 (1.9)		
Occasionally	883	768 (87.0)	67 (7.6)	48 (5.4)		
Never	279	219 (78.5)	39 (14.0)	21 (7.5)		
Sedentary hours per day					−7.66	<0.001
<8	1,503	1,365 (90.8)	100 (6.7)	38 (2.5)		
≥8	513	401 (78.1)	65 (12.7)	47 (9.2)		
Sleeping difficulty*					29.17	<0.001
Frequently	323	292 (90.4)	18 (5.6)	13 (4.0)		
Occasionally	933	777 (83.3)	108 (11.6)	48 (5.1)		
No	760	697 (91.7)	39 (5.1)	24 (3.2)		
Participate in community activities*				3.44	0.18	
Frequently	321	288 (89.7)	29 (9.0)	4 (1.3)		
Occasionally	948	817 (86.2)	95 (10.0)	36 (3.8)		
Never	747	661 (88.5)	41 (5.5)	45 (6.0)		
Number of hobbies*					0.12	0.94
≥3	380	349 (91.8)	26 (6.9)	5 (1.3)		
2	772	666 (86.3)	74 (9.6)	32 (4.1)		
≤1	864	751 (86.9)	65 (7.5)	48 (5.6)		

*Refers to Kruskal-Wallis H test; otherwise, it is Mann-Whitney U test; H/Z is the statistical parameter of Kruskal-Wallis H test and Mann-Whitney U test, respectively; The severity of ADL was classified into three levels: normal (14 scores), somewhat impaired (15–21 scores), and severely impaired (≥22 scores).

significantly affected ADL functions of older people with T2DM: eating habits ($H = 138.92$, $P < 0.001$), smoking ($H = 14.88$, $P < 0.001$), drinking ($Z = -3.28$, $P < 0.001$), doing exercise ($H = 32.82$, $P < 0.001$), sedentary lifestyle ($Z = -7.66$, $P < 0.001$), and sleeping difficulty ($H = 29.17$, $P < 0.001$). Results of trend analysis show that those eating more regularly ($Z = 17.77$, $P < 0.001$) and doing more exercise ($Z = -10.76$, $P < 0.001$) had relatively fewer ADL function restrictions.

Table 4 shows the differences in ADL functions of older people with T2DM by family characteristics. We found ADL functions were significantly affected by living conditions ($H = 28.20$, $P < 0.001$), family support ($H = 19.33$, $P < 0.001$), and family income ($H = 31.51$, $P < 0.001$). Moreover, results of trend analysis suggest that more family support ($Z = -6.07$, $P < 0.001$) and better economic status ($Z = -3.99$, $P < 0.001$) were associated with fewer ADL function restrictions.

As shown in Table 5, among the 2016 participants with T2DM, 82.7% of them lived with other chronic diseases. Moreover, the results of trend analysis suggest that those with more existing chronic diseases had more ADL function restrictions ($Z = 3.38$, $P = 0.001$). In addition to T2DM, we found the following two chronic diseases may compromise older people's ADL functions: stroke ($Z = -3.40$, $P < 0.001$) and malignant tumors ($Z = -2.63$, $P = 0.01$).

Table 6 summarizes the results of multivariate unconditional logistic regression analysis to identify factors affecting ADL functions. We found the following sub-groups were more likely to suffer from ADL impairment: those aged 70 and over years old (OR = 1.99, 95%CI 1.77–2.56), living in an aged care house or with spouse/children (OR = 2.31, 95%CI 1.25–4.26), low monthly income (OR = 1.49, 95%CI 1.28–1.64), without health insurance (OR = 1.82, 95%CI 1.40–2.40), tight family expenses (OR = 1.95, 95%CI 1.42–2.69), having stroke (OR = 6.70, 95%CI 2.22–20.23) or malignant tumor (OR = 4.45, 95%CI 1.27–15.53), irregular eating habit (OR = 2.55, 95%CI 2.23–2.92), smoking (OR = 1.40, 95%CI 1.22–1.60), sedentary lifestyle (OR = 2.04, 95%CI 1.46–2.85), lack of physical exercise (OR = 1.35, 95%CI 1.19–1.53), sleeping difficulty (OR = 1.25, 95%CI 1.10–1.42), and lack of family support (OR = 1.19, 95%CI 1.10–1.29).

Discussion

Physical disability is a major socioeconomic and public health issue, as it not only diminishes the quality of life of those affected but also may result in a greater increase in healthcare services utilization such as physician visits and hospitalizations (4, 20). Diabetes is associated with functional disability through mechanisms such as decreased cardiopulmonary reverse, inflammatory or sarcopenic process, extreme of blood glucose, muscle catabolism, cognitive impairment, and inflexible treatment regimens (5, 21–23). Presence of diabetes and associated complications can lead to a significant decline in physical functioning, especially among older patients (8, 24). Currently, there are limited studies in China investigated to what extent older T2DM patients' activities of daily living were affected and its influencing factors. The limitations in ADL and IADL have been widely used as an indicator to assess disability in basic life activities among the population over 65 years old (25, 26). In this study, we found unhealthy lifestyle

TABLE 4 Comparison of activities of daily living (ADL) functions by family characteristics in older people with type 2 diabetes in Fuzhou.

Variable	*n*	ADL			*H*	*P*-value
		Normal ($n = 1,766$)	Somewhat impaired ($n = 165$)	Severely impaired ($n = 85$)		
Living with*					28.2	<0.001
Spouse	841	759 (90.3)	60 (7.1)	22 (2.6)		
Children	298	244 (81.9)	29 (9.7)	25 (8.4)		
Spouse and children	746	646 (86.6)	66 (8.8)	34 (4.6)		
Alone	122	112 (91.8)	9 (7.4)	1 (0.8)		
Family support*					19.33	<0.001
Aged care home	9	5 (55.6)	1 (11.1)	3 (33.3)		
Very	1,208	1,088 (90.1)	91 (7.5)	29 (2.4)		
General	729	609 (83.5)	70 (9.6)	50 (6.9)		
Lack	79	69 (87.3)	4 (5.1)	6 (7.6)		
Family income*					31.51	<0.001
High	1,259	1,133 (90.0)	93 (7.4)	33 (2.6)		
Average	519	419 (80.7)	60 (11.6)	40 (7.7)		
Low	238	214 (90.0)	12 (5.0)	12 (5.0)		

*Refers to Kruskal-Wallis H test; otherwise, it is Mann-Whitney U test; H/Z is the statistical parameter of Kruskal-Wallis H test and Mann-Whitney U test, respectively; The severity of ADL was classified into three levels: normal (14 scores), somewhat impaired (15–21 scores), and severely impaired (≥22 scores).

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TABLE 5 Comparison of activities of daily living (ADL) functions by different chronic diseases in older people with type 2 diabetes in Fuzhou.

Variable	*n*	ADL			*H* /*Z*	*P*-value
		Normal (*n* = 1,766)	Somewhat impaired (*n* = 165)	Severely impaired (*n* = 85)		
Number of chronic diseases*					5.53	0.06
1	349	314 (90.0)	26 (7.4)	9 (2.6)		
2	1,274	1,119 (87.8)	107 (8.4)	48 (3.8)		
≥3	393	333 (84.7)	32 (8.2)	28 (7.1)		
Hypertension					−1.59	0.11
No	444	398 (89.6)	36 (8.1)	10 (2.3)		
Yes	1,572	1,368 (87.0)	129 (8.2)	75 (4.8)		
Coronary heart disease					−1.85	0.07
No	1,908	1,677 (87.9)	157 (8.2)	74 (3.9)		
Yes	108	89 (82.4)	8 (7.4)	11 (10.2)		
Stroke					−3.4	0
No	1,988	1,747 (87.9)	162 (8.1)	79 (4.0)		
Yes	28	19 (67.9)	3 (10.7)	6 (21.4)		
Hyperlipidemia					−0.01	0.99
No	1,879	1,646 (87.6)	154 (8.2)	79 (4.2)		
Yes	137	120 (87.6)	11 (8.0)	6 (4.4)		
Cerebrovascular disease					−1.62	0.11
No	1,995	1,750 (87.7)	162 (8.1)	83 (4.2)		
Yes	21	16 (76.2)	3 (14.3)	2 (9.5)		
Malignant tumor					−2.63	0.01
No	1,997	1,753 (87.8)	162 (8.1)	82 (4.1)		
Yes	19	13 (68.4)	3 (15.8)	3 (15.8)		
Cor pulmonale					−1.06	0.29
No	2007	1,759 (87.6)	165 (8.2)	83 (4.2)		
Yes	9	7 (77.8)	0 (0.0)	2 (22.2)		
Chronic bronchitis					−0.86	0.39
No	2000	1,753 (87.6)	164 (8.2)	83 (4.2)		
Yes	16	13 (81.3)	1 (6.2)	2 (12.5)		
Osteoarthropathy					−0.84	0.4
No	1922	1,686 (87.7)	158 (8.2)	78 (4.1)		
Yes	94	80 (85.0)	7 (7.5)	7 (7.5)		
Cataract					−1.28	0.2
No	1967	1,726 (87.7)	159 (8.1)	82 (4.2)		
Yes	49	40 (81.6)	6 (12.3)	3 (6.1)		
Glaucoma					−1.26	0.21
No	2008	1,760 (87.7)	165 (8.2)	83 (4.1)		
Yes	8	6 (75.0)	0 (0.0)	2 (25.0)		
Chronic gastroenteritis					−0.02	0.99
No	1968	1,724 (87.6)	161 (8.2)	83 (4.2)		
Yes	48	42 (87.5)	4 (8.3)	2 (4.2)		
Cholecystitis/Gallstones					−1.56	0.12
No	1982	1,739 (87.7)	162 (8.2)	81 (4.1)		
Yes	34	27 (79.4)	3 (8.8)	4 (11.8)		

(Continued)

TABLE 5 (Continued)

Variable	*n*	ADL			*H* /*Z*	*P*-value
		Normal (*n* = 1,766)	Somewhat impaired (*n* = 165)	Severely impaired (*n* = 85)		
Emphysema					−0.25	0.81
No	2009	1,760 (87.6)	165 (8.2)	84 (4.2)		
Yes	7	6 (85.7)	0 (0.0)	1 (14.3)		
Asthma					−0.42	0.68
No	2010	1,761 (87.6)	165 (8.2)	84 (4.2)		
Yes	6	5 (83.3)	0v (0.0)	1 (16.7)		
Fatty liver					−1.01	0.31
No	1983	1,739 (87.7)	161 (8.1)	83 (4.2)		
Yes	33	27 (81.8)	4 (12.1)	2 (6.1)		
Other chronic diseases					−3.37	0
No	1959	1,724 (88.0)	158 (8.1)	77 (3.9)		
Yes	57	42 (73.7)	7 (12.3)	8 (14.0)		

*Refers to Kruskal-Wallis H test; otherwise, it is Mann-Whitney U test; H/Z is the statistical parameter of Kruskal-Wallis H test and Mann-Whitney U test, respectively; The severity of ADL was classified into three levels: normal (14 scores), somewhat impaired (15–21 scores), and severely impaired (≥22 scores).

TABLE 6 Identification of factors affecting activities of daily living (ADL) limitation in older people with type 2 diabetes in Fuzhou.

Variable	Reference	Comparison group	*OR* (95%*CI*)	*P*-value
Age (years)	60–69	70–79	1.99 (1.37–2.90)	0.00
		≥80	4.78 (3.01–7.60)	0.00
Marital status	Married	Not married	2.31 (1.25–4.26)	0.01
Monthly income (Chinese Yuan)	>2,000	1,000–2,000	1.65 (1.27–2.15)	0.00
		<1,000	2.66 (2.12–3.32)	0.00
Health insurance	Covered	Partially	1.76 (0.96–3.22)	0.07
		Self-payment	3.15 (1.10–8.98)	0.03
Family expenses	Adequate	Average	1.40 (1.02–1.92)	0.04
		Tight	1.95 (1.42–2.69)	0.00
Stroke	No	Yes	6.70 (2.22–20.23)	0.00
Malignant tumor other diseases	No	Yes	4.45 (1.27–15.53)	0.02
	No	Yes	4.53 (1.90–10.83)	0.00
Eating habit	Very regular	Regular	3.35 (2.37–4.73)	0.00
		Relatively irregular	5.09 (2.90–8.96)	0.00
Smoking	No	Ex-smoker	2.08 (1.13–3.83)	0.02
Sedentary hours		Yes	2.02 (1.16–3.53)	0.01
	<8	≥8	2.04 (1.46–2.85)	0.00
Doing exercise	No	Occasionally	0.70 (0.46–1.09)	0.11
		Frequently	0.59 (0.37–0.94)	0.03
Sleeping difficulty	No	Occasionally	2.15 (1.49–3.12)	0.00
		Frequently	1.53 (0.85–2.76)	0.16
Living with	Alone	Aged care home	20.20 (3.44–118.40)	0.00
		Spouse	3.26 (1.35–7.84)	0.01
		Children	2.85 (1.26–6.44)	0.01
		Spouse and children	4.09 (1.70–9.83)	0.00

had significant impacts on older T2DM patients' functional limitations. Specifically, a high level of physical activity, being married, regular eating habits, and non-smoking are protective factors for performing ADLs. On the contrary, a sedentary

lifestyle, suffering from stroke or malignant tumor, and sleeping difficulty may increase the risk of ADL limitations among older T2DM patients. We also found that household composition was associated with physical limitations in ADLs. Participants living alone performed ADLs much better than those lived in aged care homes or living with spouse or/and children, probably because those with severe ADL impairment were lack of self-care capability and had to live with others. These findings may provide useful information for the development of nursing practice and the improvement of effective health management for older T2DM patients.

Currently, most published epidemiological research findings support that diabetes was associated with ADL limitations (27). According to a cohort study from China, the risk of ADL impairment was increased by 102% (HR = 2.02, 95%CI 1.29–3.17) for T2DM patients aged 65–74 years, compared to those without T2DM in the same age group (28). Nevertheless, inconsistency still exits. Results of a multi-country study showed that diabetes was not associated with ADL limitations in China after controlling for confounding factors such as socioeconomic status, but significant associations were found in Mexico, Barbados, Brazil, Chile, Cuba, and Uruguay (29).

In this study, we found the prevalence of functional limitations (ADL) among the older T2DM patients in Fuzhou was 12.4%. It is much lower than the national average ADL impairment rate (32.3%) according to the survey data from China Health and Retirement Longitudinal Study (CHARLS) (30, 31). The differences in the prevalence of ADL disability among T2DM patients across studies have been reported by international literature as well (8, 29), which may be due to the varied criteria used to define functional limitations. Moreover, differences in socioeconomic and healthcare services levels (e.g., early diagnosis, medical treatment, and rehabilitation) across regions/cities may also contribute to the disparity. Another possible explanation is that the CHARLS survey data were collected between 2015 and 2016, and evidence has shown that the incidence of ADL disability among the Chinese older adult population with T2DM had a declining trend over time (26), mainly due to the considerable improvements in living standard, biological environment, and healthcare services.

We found ADL limitations increased with age, as older people were more likely to experience T2DM-related comorbidities (32). Moreover, our results showed that more comorbidities were associated with a greater risk of developing ADL limitations. It is in line with previous studies (8, 26). As to gender differences in ADL limitations among T2DM patients, there is no consistency. Most previous literature suggests that older female T2DM patients usually reported more ADL functional limitations and physical disability than their male counterparts (8, 26, 28), although women generally utilized healthcare services more often than men. The greater prevalence and severity of arthritis and musculoskeletal disease among older women may partly explain the difference (33). Another explanation is that women were more likely to report or over-report their ill health and disability than men (34). However, we found males reported more ADL limitations than their female counterparts, probably because males were older than females in this study.

Our results also indicate that those living with a low socioeconomic status were at higher risk of developing functional limitations in ADLs. It is consistent with previous studies (27). Moreover, lower socioeconomic status in older age seems to predict ADL limitations more than socioeconomic status at younger age (27). In recent years, some social security programs have been launched or reformed by the government to provide better welfare to the older population, especially in health. The coverage of basic pension insurance has expanded to about one billion people in 2020 (35). Currently, there are three categories of government-funded health insurance programs, namely urban employee medical insurance, urban resident medical insurance, and new rural cooperation medical insurance, with aims to improve the accessibility for medical treatment. However, social medical insurance schemes in China adopts the "payment-before-reimbursement" principle. The insurers are required to pay the medical expenses in advance when seeking medical treatment, then a certain proportion of medical expenses are reimbursed after treatment. A large amount of prepayment may become one of the reasons restricting low-income groups from seeking timely medical treatment (36), which may potential increase risk of ADL limitations due to lack of heath care access. To reduce the healthcare burden for those with serious chronic diseases, in recent years the reimbursement cap for more than 20 chronic diseases including diabetes has been increased to 140,000 Yuan per year, compared to 6,000 Yuan for general diseases in outpatient clinics (37). Targeted supportive policies for those vulnerable subgroups are helpful for maintaining T2DM patients' ADL functions.

There are several limitations to this study. First, some older T2DM patients with severe functional limitations such as having mobility problems or staying in bed may not go to the community service center during the study period and are possibly under-represented. This may lead to the ADL function impaired rate underestimated. Second, evidence has shown that older patients in poorer health were more likely to participate in health services related research (38). Patients who gave explicit written consent may mischaracterize the health status of the larger population. In this study, we did not count how many people were excluded due to not meeting the inclusion criteria or refusing to participate. It is unclear how people who refused differ from those who agreed to participate. Therefore, the generalization of the results should be cautious due to the potential selection bias. Third, cautious should be exercised if extending the results to rural communities. Lastly, the duration of participants' diseases may be associated with

functional limitations in ADLs. However, we did not take it into account in the analysis due to unavailability issue.

Conclusion

The growing number of older T2DM patients coupled with a rapidly aging population continues to be a major public health concern in China. Older adults with T2DM especially among those aged ≥70 years had a high prevalence of functional limitations across a range of daily living tasks, which not only affect individual life of quality but also present a huge burden on the family, health services system, and the whole society. Identified factors associated with ADL limitations may provide useful information for targeted nursing practice and health promotion.

Data availability statement

The data collected during the current study is not publicly available as the ethics approval only allows for members of the research team access. Upon reasonable request and with permission of the ethics committee, access can be granted. Any queries should be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Medical Ethics Committee of Fujian Health College. The patients/participants provided their written informed consent to participate in this study.

Author contributions

J-HJ, JX, L-NJ, and H-LZ conceived the study. J-HJ, DL, and H-LZ designed the questionnaire. J-HJ, DL, L-NJ, YC, YY, and BZ did the field work and collected the data. J-HJ, DL, YC, YY, and BZ entered and cleaned the data. J-HJ, JX, and DL analyzed the data. J-HJ drafted the manuscript. JX, DL, L-NJ, YC, YY, CW, BL, RX, and H-LZ reviewed and edited the manuscript. All authors read and approved the final manuscript.

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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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Effect of metformin monotherapy and dual or triple concomitant therapy with metformin on glycemic control and lipid profile management of patients with type 2 diabetes mellitus

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Background: In this study, we aimed to compare the effects of metformin-based dual therapy versus triple therapy on glycemic control and lipid profile changes in Taiwanese patients with type 2 diabetes mellitus (T2DM).

Methods: In total, 60 patients were eligible for participation in this study. Patients received at least 24 months of metformin monotherapy, dual therapy, or triple therapy with metformin plus linagliptin (a dipeptidyl peptidase 4 (DPP-4) inhibitor) or dapagliflozin (a sodium-glucose cotransporter-2 (SGLT2) inhibitor). Blood samples were collected from each patient, followed by evaluation of changes in their blood glucose control and lipid profile-related markers.

Results: A combination of metformin and DPP4 and SGLT2 inhibitor therapy more effectively reduced low-density lipoprotein cholesterol (LDL-C) (p = 0.016) than metformin monotherapy. A combination of metformin and DPP4 and SGLT2 inhibitor therapy more effectively improved total cholesterol (Chol, p = 0.049) and high-density lipoprotein cholesterol (HDL-C) than metformin monotherapy (p = 0.037). Metformin plus linagliptin dual therapy was more effective than metformin monotherapy in reducing glycosylated hemoglobin (HbA1C, p = 0.011). Patients who received a combination of linagliptin and empagliflozin showed a significant reduction in their fasting blood glucose (p = 0.019), HbA1c (p = 0.036), and Chol (p = 0.010) compared with those who received linagliptin dual therapy. Furthermore, patients who

received metformin plus dapagliflozin and saxagliptin showed significantly reduced Chol (p = 0.011) and LDL-C (p = 0.035) levels compared with those who received metformin plus dapagliflozin.

Conclusion: In conclusion, dual therapy with metformin and linagliptin yields similar glycemic control ability to triple therapy. Among metformin combination triple therapy, triple therapy of empagliflozin and linagliptin might have a better glycemic control ability than dual therapy of linagliptin. Moreover, Triple therapy of dapagliflozin and saxagliptin might have a better lipid control ability than dual therapy of dapagliflozin.

KEYWORDS

type 2 diabetes mellitus, metformin, glycemic control, lipid profile, concomitant therapy

Introduction

Asia is considered the epicenter of the global epidemic of type 2 diabetes mellitus (T2DM) because of rapid changes in eating habits and lifestyle and the increasing rates of obesity in Asia (1). Many studies have reported the epidemic of T2DM in East Asia and the interethnic differences in genetics, pathophysiology, eating habits, and lifestyle factors between Asian regions and also between Asian and Western countries (2).

Type 2 diabetes mellitus is characterized by chronic hyperglycemia and disturbances of carbohydrate, lipid, and protein metabolism. To date, patients with T2DM who initially achieve glycemic control with a single oral antidiabetic medicine usually require additional agents for maintaining glycemic control due to the progressive nature of the disease (3).

Several studies have verified the correlation between blood glucose levels and serum lipid profiles (4). Thus, use of an appropriate and cost-effective medication for T2DM is recommended. Concomitant use of multiple medicines is often indicated in the management of diseases; however, more medicines might not necessarily be better. Polypharmacy could result in increased healthcare costs and risks of adverse drug events and medication non-adherence (5). Therefore, to compare and confirm the different effects of monotherapy, dual therapy and triple therapy on lipid profiles and glucose control is important under the premise of minimizing side effects.

Metformin is recommended as a first-line oral glucose-lowering medication by the American Diabetes Association (6). It is usually prescribed along with other antidiabetic drugs such as sodium-glucose cotransporter-2 (SGLT2) inhibitors and dipeptidyl peptidase 4 (DPP4) inhibitors to control blood glucose and lipid levels. However, few studies have evaluated the efficiency of different types of metformin-based therapies in glycemic control and lipid profile management and compared them with metformin-based dual (with an SGLT2 inhibitor or a DPP4 inhibitor) and triple therapy (metformin with an SGLT2 inhibitor and a DPP4 inhibitor) in Taiwanese patients. Therefore, in the present study, we aimed to compare the effects of different types of metformin-based therapies on glycemic control and lipid profile changes in Taiwanese patients with T2DM.

Materials and methods

Patients

This study was conducted at Taipei Medical University Hospital, Taiwan. Participants who visited the endocrinology outpatient department between October 2021 and March 2022 were screened for eligibility. Individuals were eligible if they were above 20 years of age; had T2DM; who received at least 24 months of metformin monotherapy or combination therapy with linagliptin (DPP4 inhibitor) or dapagliflozin (SGLT2 inhibitor); and were on regular follow-up for blood tests for glucose, glycosylated hemoglobin (HbA1c), and lipid profile. Patients were excluded if they were receiving insulin injections or lipid-lowering drugs, such as statin. Individuals with renal or hepatic dysfunction or failed blood glucose control were also ineligible.

The study screened 85 individuals for eligibility. Of these patients, 18 patients were excluded, because they were prescribed lipid-lowering drugs, and 7 were excluded, because they were prescribed insulin injections. **Figure 1** details the number of participants enrolled in the study along with the reason for exclusion of some participants. Finally, the study enrolled 60 participants whose demographic features have been summarized.

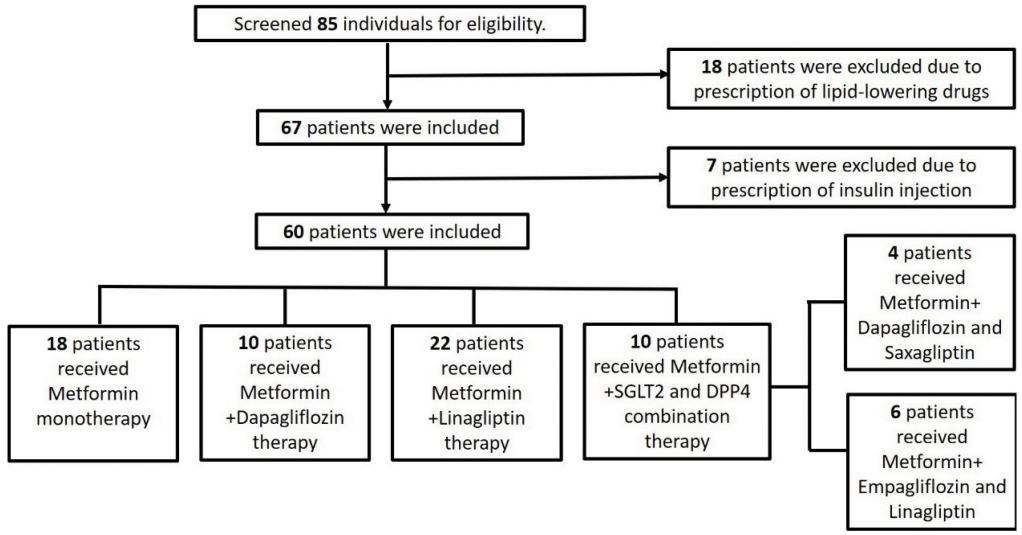

FIGURE 1
Flowchart showing patient inclusion in the study.

All patients provided their written informed consent prior to enrolment. The study protocol was approved by the ethics committee of the Institutional Review Board of Taipei Medical University (Approval No: N202107021). All procedures accorded with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration.

Patient grouping and assignment

Patients were divided into four groups according to the treatment they received: metformin 1,000 mg monotherapy (metformin only group, N = 18); metformin 1,000 mg and linagliptin 5 mg combination therapy (+ DPP4 group, N = 22); metformin 1,000 mg and dapagliflozin 10 mg combination therapy (+ SGLT2 group, N = 10); and either metformin 1,000 mg plus empagliflozin 10 mg and linagliptin 5 mg or dapagliflozin 10 mg and saxagliptin 5 mg combination therapy (+ SGLT2 and DPP4 group, N = 10).

The 10 patients who received DPP-4 inhibitor and SGLT-2 inhibitor combination therapy (triple therapy) included 6 patients with empagliflozin 25mg and linagliptin 5 mg and 4 patients with dapagliflozin 10mg and saxagliptin 5mg.

Medicinal compliance

Medication compliance was evaluated by the self-report of remain pill count. When patients come back to follow up, we calculated remain pills from self-report. And remain doses of medicine were record.

Hematological analysis

Routine blood tests were performed at the clinical laboratory. Blood samples were collected from each patient after an overnight fast. Serum uric acid and ketone levels were determined using a one-touch self-metabolic marker monitoring analyzer (FORA MD-6; Fora Care, Taipei, Taiwan). Fasting glucose (glucose AC) was analyzed according to the hexokinase method (ADVIA Chemistry XPT System, Siemens, Berlin, Germany), and HbA1c was determined by high-performance liquid chromatography using an automatic analyzer (Bio-Rad Variant II Turbo 2.0 System, Hercules, California, USA). Serum lactate dehydrogenase (LDH), C- peptide, creatine (Cr), Alanine aminotransferase (ALT), total cholesterol (Chol), triglyceride (Tg), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels were analyzed by enzymatic methods using an automatic analyzer (ADVIA Chemistry XPT). Serum insulin antibody (insulin Ab) was measured by immunoradiometric binding assay in an automatic analyzer (PerkinElmer CSBio, Santa Clara, California, USA).

Modified homeostasis model assessment-insulin resistance index

Homeostasis model assessment-insulin resistance index is a simple and useful method for evaluating insulin resistance. Modified HOMA-IR was calculated using the following equation: 1.5 + fasting blood

glucose × fasting C-peptide/2,800 (7, 8). A result above 1.9 indicated early insulin resistance, whereas a result above 2.9 indicated significant insulin resistance (7, 8).

Statistical analysis

Statistical analysis and data management were performed using IBM SPSS Statistics 22 (IBM Corp., Armonk, NY, USA). Data are expressed as the mean and median. The Chi-square test was used for results of nominal scale. Data distributions were analyzed by Shapiro-Wilks test for normality. Non-parametric statistics, which are Mann–Whitney U test with Kruskal-Wallis Test were used to determine whether any between-group differences existed in the groups of patients, the *post hoc* test was using Dunn *post hoc* test. The Wilcoxon signed-rank test was used to analyze the within-group differences in the paired results of patients. A confidence interval of 95% was employed, and p <0.05 indicated statistical significance.

Results

Baseline characteristics and comparisons between study groups

A total of 60 participants with T2DM who received different medication therapies were included. The statistical results indicated no significant difference between the groups of patients who received different therapies in T2DM duration, body mass index (BMI), age, fasting blood glucose, HbA1c, LDH, and HOMA-IR score and levels of insulin Ab, C-peptide, uric acid, ketone, Cr, and ALT (**Table 1**).

Between-group analysis of changes in lipid profiles

A significant difference was observed in the lipid profiles of patients in the metformin only group and the + SGLT2 and DPP4 group in terms of Chol (p = 0.033), HDL-C (p = 0.011), and LDL-C levels (p = 0.015). As indicted in **Table 2**, significantly different changes were observed in serum Chol (p = 0.010) between the + SGLT2 and DPP4 group and the DPP4 group. Similarly, significantly different changes were observed in Chol (p = 0.002) and LDL-C (p = 0.008) levels between patients treated with + SGLT2 and DPP4, and SGLT2.

Within-group analysis of lipid profiles before and after treatment in each group

The metformin monotherapy group exhibited significantly reduced levels of GPT (p = 0.01), Chol (p = 0.01), and LDL-C (p = 0.001) after treatment. Moreover, the metformin combined with linagliptin (+ DPP4) group exhibited significantly reduced Glucose AC (p = 0.035) and HbA1c (p = 0.019) relative to the pretreatment treatment. Similarly, the + SGLT2 and DPP4 group exhibited significantly reduced fasting blood Glucose (p = 0.035), HbA1c (p = 0.019), GPT (p = 0.007), Chol (p = 0.035), and Tg (p = 0.045) levels relative to the pretreatment values. The changes in lipid profile are presented in **Table 2**.

Effect of different combination therapies on lipid profile and blood glucose control

To further verify the effect of metformin plus empagliflozin and linagliptin and metformin plus dapagliflozin and saxagliptin in the + SGLT2 and DPP4 group, the groups of patients receiving metformin plus linagliptin and empagliflozin and those receiving metformin plus linagliptin treatment were analyzed. A significant difference was observed in the fasting blood *glucose* (p = 0.019) and HbA1c (p = 0.036) levels (**Table 3**) between patients receiving linagliptin and those receiving empagliflozin with linagliptin. Similarly, a significant difference was observed in Chol (p = 0.019) and LDL-C levels (p = 0.035) (**Table 4**) between patients who received dapagliflozin and saxagliptin.

Medicinal compliance

When calculated remain pills from self-report (since last 3 months), mean remain dose by drug was not statistically different each group. The remain medicine dose of groups were 1.9 (median: 2.0), 1.0 (median: 1.0), 2.0 (median: 2.5) and 2.4 (median: 2.0) doses (p = 0.132), respectively (data not shown).

Discussion

The main finding of this study is that although a combination of metformin with a DPP4 and an SGLT2 inhibitor more effectively improved Chol and LDL-C than a combination of metformin and linagliptin or dapagliflozin dual therapy did. However, a similar effect also was found on reducing fasting glucose and HbA1C levels with metformin and linagliptin dual therapy.

TABLE 1 Between-group analysis of clinical characteristics of the patients with type 2 diabetes mellitus (T2DM).

		Metformin										
	Reference range	Metformin Only(N = 18)		+ SGLT2(N = 10)			+DPP4 (N = 22)			+ SGLT2 and DPP4 (N = 10)			Sig.
		MEAN	Median	MEAN	Median	*p*	MEAN	Median	*p*	MEAN	Median	*p*	
Male (%)	–	55.0	–	80.0	–	0.063	68.0	–	0.292	80.0	–	0.119	0.206
Duration of T2DM (Month)	–	68.9	73.3	70.5	81.0	0.849	62.9	74.3	0.486	69.8	68.0	0.457	0.864
BMI	–	27.2	27.3	30.9	28.5	0.156	27.9	27.1	0.909	27.0	27.1	0.855	0.440
Age	–	55.1	54.0	52.5	53.0	0.787	55.0	54.0	0.292	60.5	64.0	0.332	0.430
Glucose Ac	<100 mg/dl	172.1	139.0	185.3	156.5	0.641	145.9	146.0	0.537	176.7	173.5	0.291	0.301
HbA1c	<5.5%	7.9	7.2	7.6	6.8	0.723	7.2	6.7	0.389	7.4	7.3	0.614	0.667
LDH	98-192U/L	199.1	179.0	196.3	185.0	0.755	195.0	198.0	0.577	202.0	175.0	0.549	0.775
Insulin Ab	<7.5%	5.9	6.0	6.2	5.6	0.675	6.1	6.1	0.437	5.6	5.2	0.597	0.726
C-peptide	0.8-3.8ng/mL	2.8	2.5	3.7	3.5	0.113	3.2	3.1	0.800	2.7	2.3	0.684	0.256
HOMA-IR	<1.9	1.7	1.6	1.7	1.7	0.573	1.7	1.6	0.393	1.7	1.6	0.924	0.676
Uric acid	0.24-0.51 μmol/L	352.8	102.0	341.0	148.0	0.851	334.9	128.1	0.803	335.5	330.1	0.100	0.997
Ketone	< 0.6 mmol/L	0.7	0.7	0.6	0.7	0.904	1.0	0.5	0.281	0.5	0.5	0.406	0.445
Cr	0.7-1.2 mg/dl	0.9	0.9	0.9	0.8	0.884	1.5	1.0	0.127	0.9	0.9	0.563	0.404
ALT	< 40U/L	24.2	23.0	31.0	28.0	0.371	30.3	28.0	0.166	28.0	28.5	0.350	0.605

DPP-4: dipeptidyl peptidase-4 inhibitor; SGLT-2: sodium glucose transporter-2; BMI; LDH: lactate dehydrogenase; Glucose AC: fasting blood glucose; HbA1c: glycosylated hemoglobin; C-peptide: C-reactive peptide; insulin Ab: insulin antibodies; HOMA-IR: Homeostasis Model Assessment-Insulin Resistance Index; Cr: creatinine; ALT: Alanine Aminotransferase.

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TABLE 2 Within-group analysis of glycemic control- and lipid profile-related biomarkers before and after treatment in each group.

		Metformin											
	Reference range	Metformin Only		+ SGLT2			+DPP4			+ SGLT2 and DPP4			Sig.
		MEAN	Median	MEAN	Median	*p*	MEAN	Median	*p*	MEAN	Median	*p*	
Glucose AC (B)	< 100mg/dl	200.9	117.1	235.2	164.5	0.092	290.3	23.3	0.448	239.9	95.0	0.266	0.708
Glucose AC		172.1	77.4	185.3	84.9	0.641	145.9	43.3	0.537	176.7	48.5	0.291	0.301
Δ		−28.8			−49.9		−144.4				-63.2		
p		0.064			0.297			0.009**			0.035*		
HbA1c (B)	< 5.5%	8.8	2.9	8.5	2.9	0.675	8.6	2.6	0.810	7.8	1.9	0.769	0.982
HbA1c		7.9	2.7	7.6	2.0	0.723	7.2	1.4	0.389	7.4	1.2	0.614	0.667
Δ		−0.9			−0.8			−1.4			−0.5		
p		0.077			0.233			0.042*			0.019*		
Chol (B)	< 5.2 mmol/L	5.6	5.3	5.1	5.3	0.100	4.5	4.7	0.900	4.3	4.6	0.085	0.123
Chol		4.2	4.2	4.5	4.5	0.378	4.3	3.7	0.842	3.3	3.2	0.033*	0.010*
Δ		−1.4			−0.6			−0.2			−1.1		
p		0.002**			0.114			0.044*			0.049*		
Tg (B)	< 1.69 mmol/L	2.4	2.0	1.8	1.7	0.306	2.1	1.6	0.418	1.7	1.7	0.308	0.699
Tg		1.6	1.4	1.7	1.7	0.535	1.9	1.2	0.433	1.2	1.0	0.792	0.197
Δ		−0.8			−0.1			−0.2			−0.5		
p		0.035*			0.812			0.169			0.037*		
HDL-C (B)	> 1.53 mmol/L	1.0	1.0	1.2	1.2	0.085	1.1	1.1	0.269	1.0	1.0	0.456	0.171
HDL-C		1.1	1.1	1.2	1.2	0.113	1.2	1.2	0.522	1.2	1.2	0.011*	0.461
Δ		0.1			0.0			0.0			0.1		
p		0.115			0.492			0.316			0.160		
LDL (B)	< 2.6 mmol/L	3.5	3.3	3.4	3.8	0.826	2.7	2.5	0.350	2.6	2.8	0.500	0.057
LDL-C		2.6	2.5	2.8	2.8	0.616	2.4	2.0	0.431	1.5	1.6	0.015*	0.016*
Δ		−0.8			−0.6			−0.3			−1.1		
p		0.002**			0.097			0.017*			0.176		

B: before treatment result; Glucose AC: fasting blood glucose; HbA1c: glycosylated hemoglobin; Chol: total cholesterol; Tg: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol. Δ: difference between the before treatment result and recent result. *$p < 0.05$; **$p < 0.01$. Red values indicate significant differences.

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TABLE 3 Effects of metformin with linagliptin dual therapy and metformin with linagliptin and empagliflozin triple therapy on lipid profile and blood glucose control of patients with type 2 diabetes mellitus.

	Reference range	Metformin				
		+ DPP4 (Linagliptin)		+SGLT2 and DPP4 (Empagliflozin and Linagliptin)		*p*
		MEAN	Median	MEAN	Median	
Duration of T2DM (Month)	–	62.9	66.8	58.35	68.00	0.783
Glucose AC (B)	< 100mg/dl	290.3	23.3	234.8	118.7	0.586
Glucose AC		145.9	43.3	128.7	31.50	0.019*
Δ		−144.4		−106.2		
p		0.009**		0.543		
HbA1c (B)	< 5.5%	8.6	2.6	7.8	1.93	0.487
HbA1c		7.2	1.4	6.7	0.91	0.036*
Δ		−1.4		−1.1		
p		0.042*		0.646		
Chol (B)	< 5.2 mmol/L	4.5	4.7	4.4	4.15	0.445
Chol		4.3	3.7	3.4	3.08	0.010*
Δ		−0.2		−1.0		
p		0.044*		0.014*		
Tg (B)	< 1.69 mmol/L	2.1	1.6	1.9	1.81	0.814
Tg		1.9	1.2	1.5	1.47	0.245
Δ		−0.2		−0.5		
p		0.2		0.619		
HDL-C (B)	> 1.53 mmol/L	1.1	1.1	0.9	0.96	0.112
HDL-C		1.2	1.2	1.2	1.1	0.847
Δ		0.1		0.3		
p		0.316		0.848		
LDL-C (B)	< 2.6 mmol/L	2.7	2.5	2.5	2.04	0.588
LDL-C		2.4	2.0	1.9	1.67	0.124
Δ		−0.3		−0.6		
p		0.017*		0.274		

BH: body height; BW: body weight; LDH: lactate dehydrogenase; Glucose AC: fasting blood glucose; HbA1c: glycosylated hemoglobin;Chol: total cholesterol; Tg: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol. *$p < 0.05$, **$p < 0.01$. Red values indicate significant differences.

Although the reasons for high or low medication adherence differ among patients, complicated regimens and a larger number of medications can reduce compliance (9). Compliance to therapy is important point in chronic conditions. Methods of measuring adherence can be either direct (biological marker) or indirect (self-reporting, questionnaires, pill counts) (10). Therefore, we calculated the remain dose of pills when every return visit for ensure homogeneity of study population. Base on the remain pill counts form study population by self-report, we ensured treatment compliance homogeneity of study population in groups.

Metformin is the first-line treatment for individuals with newly diagnosed T2DM. Our study corroborated previous findings that metformin monotherapy considerably improves dyslipidemia in statin-naive individuals with T2DM (11), especially by reducing serum LDL-C *via* an AMP-activated protein kinase pathway (12). Metformin has been reported to improve insulin sensitivity by increasing it; it also reduces the rate of lipolysis, thereby decreasing the conversion of free fatty acids in the liver (13). A previous meta-analysis showed that metformin reduced body weight and improved the lipid profiles of 60-year-old participants. The results also suggest that metformin treatment may reduce the risk of major coronary events and all-cause mortality in diabetic populations (14).

The mechanism through which DPP4 inhibitors affect the lipid profile in T2DM remains poorly understood. This effect could be explained by glucagon-like peptide-1 receptor. DPP4 inhibitors might inhibit lipid absorption in the gastrointestinal tract. The action of DPP4 inhibitors is based on their prevention of the inactivation of incretin. A previous study reported that these compounds improve glycemic control, both when applied in monotherapy and in combination with other oral hyperglycemic agents. Patients with different levels of glycemic control who received DPP4 inhibitors combined with

TABLE 4 Effects of metformin with dapagliflozin dual therapy and metformin with dapagliflozin and saxagliptin triple therapy on lipid profile and blood glucose control in patients with type 2 diabetes mellitus.

	Reference range	Metformin				
		+ SGLT2 (Dapagliflozin)		+SGLT2 and DPP4 (Dapagliflozin and Saxagliptin)		*p*
		MEAN	Median	MEAN	Median	
Duration of T2DM (Month)	–	70.46	76.2	74.7	74.7	0.542
Glucose AC (B)	< 100mg/dl	235.2	164.5	242.5	253.0	0.933
Glucose AC		185.3	84.9	182.5	24.4	0.888
Δ		−49.9		−60.0		
p		0.297		0.984		
HbA1c (B)	< 5.5%	8.5	2.9	9.1	8.9	0.656
HbA1c		7.6	2.0	8.4	8.30	0.963
Δ		−0.8		−0.7		
p		0.233		0.900		
Chol (B)	< 5.2 mmol/L	5.1	5.3	4.7	4.87	0.336
Chol		4.5	4.5	3.3	3.28	0.011*
Δ		−0.6		−1.4		
p		0.114		0.309		
Tg (B)	< 1.69 mmol/L	1.8	1.7	1.4	1.27	0.520
Tg		1.7	1.7	1.2	0.90	0.133
Δ		−0.1		−0.2		
p		0.812		0.824		
HDL-C (B)	> 1.53 mmol/L	1.2	1.2	1.1	1.00	0.817
HDL-C		1.2	1.2	1.1	1.10	0.606
Δ		0.0		0.0		
p		0.492		0.168		
LDL-C (B)	<2.6 mmol/L	3.4	3.8	2.8	3.10	0.354
LDL-C		2.8	2.8	1.5	1.70	0.035*
Δ		−0.6		−1.3		
p		0.097		0.120		

Glucose AC: fasting blood glucose; HbA1c: glycosylated hemoglobin; Chol: total cholesterol; Tg: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol. *$p < 0.05$. Red values indicate significant differences.

metformin therapy exhibited reduced fasting blood glucose and HbA1C levels compared with those who received continuous therapy with metformin alone (15). This result is consistent with our findings in presented study.

Previous findings have indicated that individuals from East Asia have lower insulin resistance and greater sensitivity to the incretin effect (16). In particular, the glucose control efficacy of DPP4 inhibitors or incretin receptor agonists has been reported to be greater in Asian populations, especially Japanese (17) and Korean populations (18). The difference in the treatment responses could be ascribed to a different lower insulin secretory function and less insulin resistance in T2DM or the different genetics in these populations. Previous results show that DPP4 inhibitors achieve good glucose control in the Asian population (19). This result is consistent with our findings in a Taiwanese population. However, in our study, the triple therapy group also showed good glucose control and lipid profile effects.

Dyslipidemia is associated with an increased risk of cardiovascular disease in patients with T2DM. Previous studies have also suggested that the lipid-reducing efficiency of linagliptin or metformin may be lower than that of dapagliflozin (20) and a placebo (21). The different effects of monotherapy, dual therapy, and triple therapy with metformin on the lipid profiles of patients with T2DM in this study are largely consistent with the results of previous studies (22–24). In our study, triple therapy reduced the lipid profile as effectively as linagliptin dual therapy did, there were also significant differences when compared with metformin monotherapy. However, the mean Chol, HDL-C, and LDL-C levels significantly differed from baseline to after treatment DPP4 and SGLT2 inhibitor combination therapy (62.9 months on average).

In terms of blood glucose control, early combination treatment with linagliptin and metformin has been reported

to improve hyperglycemia, resulting in a significant reduction in fasting glucose relative to that achieved after metformin monotherapy (25). Another study reported that compared with linagliptin monotherapy, linagliptin plus metformin treatment significantly reduced HbA1c levels after 24 weeks relative to the baseline levels (26). According to present results, similar to triple therapy, linagliptin dual therapy could improve blood glucose and HbA1C levels.

Previous studies reported that combination therapy with empagliflozin, linagliptin, and metformin (22) or dapagliflozin, saxagliptin, and metformin (27) produced considerable glucose-lowering effects in patients with T2DM. In a 52-week study, reductions in HbA1c with empagliflozin plus linagliptin therapy were superior to those with the joint use of either empagliflozin or linagliptin with metformin (28). To further verify this effect, we classified patients in the metformin triple therapy group into two different groups and reanalyzed the findings. We found that the addition of empagliflozin to metformin plus linagliptin led to a more effective reduction in fasting glucose, HbA1C l and Chol levels.

Moreover, the addition of saxagliptin to metformin plus dapagliflozin therapy led to a more effective reduction in serum Chol and LDL-C levels (**Table 4**). The results may indicate that a combination of metformin plus both linagliptin and saxagliptin affects the lipid profile in a manner different from that observed when a combination of metformin plus both empagliflozin and dapagliflozin is used. In other words, our results suggest that empagliflozin might have a better glycemic control ability than dapagliflozin. The results showed improvement in fasting glucose and HbA1C levels similar to that in a previous study (29) and demonstrated that saxagliptin might afford better LDL-C control than linagliptin. In the results of previous cross-sectional study, saxagliptin users had a significantly lower CVD risk than other DPP-4 drug users matched for sex, age, duration of drug use, systolic blood pressure, lipid profile, and fasting glucose (30). However, further large-scale observational studies evaluating the differences among these drugs is in terms of their cardiovascular benefits or glucose control abilities are needed.

This study has some limitations. First, our study was conducted at a single center, and the sample size was relatively small. Second, owing to the retrospective nature of the study, the medication history of the participants was not controlled, and whether the participants had ever been prescribed other antidiabetic medicines with varying drugs was unclear. Therefore, the interaction effects or side effects of the drugs may have been underestimated. Third, because this study only involved Taiwanese people, ethnic differences could not be accounted for. Thus, we followed a strict patient selection protocol to ensure homogeneity between groups. Further studies are needed to apply the results of this study to larger populations.

Conclusion

In conclusion, we report that dual therapy with metformin and linagliptin yields similar glycemic control ability to triple therapy. Among metformin combination triple therapy, triple therapy of empagliflozin and linagliptin might have a better glycemic control ability than dual therapy of linagliptin. Moreover, Triple therapy of dapagliflozin and saxagliptin might have a better lipid control ability than dual therapy of dapagliflozin.

Combination therapy of metformin with an SGLT2 inhibitor and a DPP4 inhibitor may be an effective, but albeit relatively expensive, treatment for patients with T2DM. Thus, based on the results, dual therapy with metformin and linagliptin may be a better option for long-term glycemic control because of the similar glucose control ability to triple therapy. Further studies should investigate the long-term efficacy and cost-effectiveness of each combination therapy. These results could provide a guide for clinical physicians to select a more appropriate prescription from metformin monotherapy, dual therapy, or triple therapy in the future.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Research Ethics Committee of Institutional Review Board of Taipei Medical University (Approval No: N202107021). The patients/participants provided their written informed consent to participate in this study.

Author contributions

Y-SH and Y-YL designed this study, collected and analyzed the data. Y-SH, Y-YL, and S-FW wrote the main manuscript. C-HH, C-LH, and Y-PL revised the manuscript. M-CY and A-YH reviewed the manuscript and provided the recommend in study design. All authors reviewed the manuscript.

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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Analysis of magnetic resonance splectroscopy characteristics in patients with type 2 diabetes complicated with stroke

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In this study, we investigated the metabolism of white matter by magnetic resonance spectroscopy (MRS) in stroke complicated with diabetes mellitus in combination with glycosylated hemoglobin (HbAlc) detection and clinical neurological deficit score (NIHSS). Fifty-three patients with stroke within 24 h after onset were collected and scanned by MRS. The biochemical, clinical and imaging characteristics of patients were analyzed. Patients were divided into three groups according to HbAlc levels: Good glycemic control (A): < 6.5%; satisfactory glycemic control (B): 6.5–7.5% and poor glycemic control (C): > 7.5%. The results showed that HbA1c levels were positively correlated with NIHSS in patients with acute ischemic stroke (AIS). There is significant difference in NAA/Cr between the infarcted site of the three groups and the mirror site. HbA1C level was negatively correlated with NAA/Cr in patients with AIS, and there was no significant correlation between NIHSS score and NAA/Cr. The data above demonstrated that the MRS imaging can be used to explain the adverse effects of hyperglycated hemoglobin on brain parenchyma from the perspective of imaging. This imaging technique and clinical NIHSS score have a high consistency in evaluating stroke.

KEYWORDS

ischemic stroke, hydrogen proton magnetic resonance imaging, glycosylated hemoglobin, NIHSS score, NAA/Cr

Introduction

Stroke is a cerebrovascular disease with high morbidity, mortality and disability. Diabetes is one of the independent risk factors for stroke (1–3). Diabetes patients are 2–6 times more likely to have a stroke than non-diabetics and the risk of recurrent stroke is also doubled (4, 5). Stroke patients combined with diabetes are more prone

to recurrence and deterioration (4), and clinicians are required to urgently evaluate patients with appropriate imaging methods. Traditional neuroimaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT), can only show morphological changes after stroke (6) but cannot reveal the feature of nerves and biochemicals. In this study, magnetic resonance spectroscopy (MRS) was used to study the metabolism of white matter in patients with Type 2 diabetes Complicated with Stroke. Taking into consideration glycosylated hemoglobin and clinical neurological deficit score (NIHSS), biochemical and clinical analysis of diabetic patients who suffered a stroke was analyzed. By studying the characteristic evolution of the imaging, we can establish as early warning mechanism, which could eventually provide valuable information for the clinical treatment of cerebral infarction and for the evaluation of prognosis (7–9).

Subjects and methods

General information

We searched the database of Shanghai Pudong New Area Gongli hospital for patients who were admitted in the department of neurology between June 2015 to June 2017. The DWI imaging system had 53 patients with single stroke in the basal ganglia, which were included in the study. All patients included in this study were primary cerebral infarction. Inclusion criteria were as follows: Patients who met the 2014 edition of guidelines for the diagnosis and treatment of acute ischemic stroke (AIS) in China; exclusion criteria: hypertension, hyperlipidemia, brain injury patients and other neurological diseases, magnetic resonance imaging contraindications (patients with pacemakers, patients with nerve stimulators, artificial metal heart valves, intraocular metal foreign bodies, inner ear implants, *in vivo* ferromagnetic foreign bodies; early pregnancy—within first 3 months of pregnancy; severe Hyperthermia) and also patients who are claustrophobic.

Subjects signed informed consent.

Instruments and methods

The TOSHIBA EXCELART Vantage 1.5T magnetic resonance imaging instrument is equipped with an 8-channel head and neck coil. All subjects underwent routine MRI (T1WI, T2WI, FLAIR) sequence, diffusion weighed imaging (DWI) and MRS examination.

DWI was as follows: SE sequence, TE1550 ms, matrix 128 × 128, FOV 24 × 24, layer thickness 5.5 mm, layer spacing 1.0 mm, *b*-value 1,000 s/mm^2.

MRS characteristics was as follows: Multi-voxel acquisition using point-resolved spectroscopy (PRESS). General parameters: TR 1,500 ms, TE 136 ms, average number of 1, and detection time: 6:15 min.

Volume of interest (VOI) Selection: According to the high sensation area of the basal ganglia on the DWI, the acute infarct area was used as the VOI. The sampling volume is based on 15 mm × 15 mm × 15 mm. According to the size of the lesion to be detected, the lesion area should be included in one voxel as much as possible, and we tried to avoid the interference of the skull, fatty tissue and cerebrospinal fluid.

Within 24 h of admission, the author used the National Institutes of Health Stroke Scale (NIHSS score) to score neurological deficits in patients. The grading was done as follows: mild impairment: NIHSS $\leq$ 6 points, moderate impairment: 6–16 points, severely affected: $\geq$ 16 points. As far as possible, we did not repeat our instructions or make the patients do the same movement twice (such as repeatedly asking the patient to do some kind of effort). The time taken to score the patient was not more than 2 min.

Venous blood was collected within 24 h after admission, and glycated hemoglobin (HbA1c) was detected by high pressure liquid chromatography. According to the 2013 American Diabetes Association, Diagnosis and classification of diabetes mellitus (7), HbA1C $\geq$ 6.5% is listed as Diagnostic criteria for diabetes. Blood glucose control is grouped according to glycated hemoglobin levels. Good glycemic control group (group A): HbAlc < 6.5%; Satisfactory glycemic control group (group B): HbAlc: 6.5∼7.5%; poor glycemic control group (group C): HbAlc > 7.5%.

Statistical analysis

The data was analyzed using statistical software SPSS22.0. The *t*-test and analysis of variance were used to compare the general data, NIHSS score and MRS parameters of the three groups. The correlation between NIHSS score and HbAlc, the correlation between NIHSS score and MRS parameters of the three groups were analyzed by Pearson correlation (when $|r| \geq$ At 0.8, it was considered that the two variables are highly correlated; when $0.5 \leq |r| \leq 0.8$, the two variables were considered to be moderately related; when $0.3 \leq |r| \leq 0.5$, the two variables were considered to have a low correlation. When $0 \leq |r| \leq 0.3$, the degree of correlation is weak and basically irrelevant). $P < 0.05$ was considered statistically significant.

Results

General information comparison

The clinical characteristics of 53 stroke patients in this study are shown in **Table 1**. There were no

significant differences in gender and mean age between the three groups ($P = 0.1$, $P = 0.5$). The three groups were investigated for metabolic indicators such as low-density lipoprotein, fasting blood glucose, and HbAlc. The differences were statistically significant ($P < 0.05$, $P < 0.01$, $P < 0.01$).

Neurological function score

The NIHSS scores of the three groups are shown in Table 2. The NIHSS scores of the three groups were compared. Group A: 3.6129 ± 3.56537, Group B: 4.6667 ± 2.59808, Group C: 6.4615 ± 2.81707, the difference was statistically significant ($P < 0.05$).

HbA1C levels and NIHSS scores of the three groups A, B, C were compared, Pearson correlation analysis showed that patients with AIS had a positive correlation between blood HbA1C levels and NIHSS ($r = 0.276$, $P \leq 0.05$), that is, the higher the HbA1C level, the higher the NIHSS score (Figure 1).

Changes in magnetic resonance spectroscopy metabolites

In group A, B, C, the metabolites of the site of infarcts and their contralateral mirror site were compared (see Table 3). In Group A infarct side NAA/Cr: 1.09 ± 0.22, mirror side NAA/Cr: 1.67 ± 0.36, $t = -7.647$; Group B infarct side NAA/Cr: 0.91 ± 0.14, mirror side NAA/Cr: 1.16 ± 0.24, $t = -2.618$; Group C infarct side NAA/Cr: 0.87 ± 0.21, mirror side NAA/Cr: 1.16 ± 0.26, $t = -3.098$, the difference was statistically significant ($P < 0.01$, < 0.05, < 0.05), and for the Cho/Cr ratio the difference was not statistically significant ($t = -2.261$, -1.842, -4.522, $P < 0.05$, $= 0.05$, < 0.05), Lac appeared 25 times in total.

Comparison of metabolites between infarcts in patients of group A, B and C: There was a significant difference in NAA/Cr ($P < 0.01$) but there was no significant difference in Cho/Cr ($P > 0.05$). The difference in Lac/Cr was statistically significant ($P < 0.05$).

The blood HbA1C and NIHSS scores of patients in group A, B and C were compared with respect to NAA/Cr, Cho/Cr and Lac/Cr values. Pearson correlation analysis showed that blood HbA1C levels had a low negative correlation with NAA/Cr ($r = -0.494$, $P \leq 0.01$, it had a low negative correlation with Cho/Cr ($r = -0.354$, $P \leq 0.01$), and the correlation with Lac/Cr was not statistically significant ($r = 0.252$, $P = 0.1$). There was no significant correlation between NIHSS score and NAA/Cr, Cho/Cr, and Lac/Cr ($r = -0.135$, $r = -0.004$, $r = 0.164$, $P = 0.1$) (Figures 2, 3).

Discussion

Application of magnetic resonance spectroscopy in stroke patients

The 1H-MRS detection index usually includes nitrogen-acetylaspartate (NAA), choline complex (Cho), creatine (Cr), and lactic acid (Lac) (10, 11). The ratio of NAA/Cr and Cho/Cr reflects the change of NAA and Cho concentration to some extent. To a certain extent, it can be used for the diagnosis and evaluation of diseases (12–14).

In this experiment, 53 patients with acute cerebral infarction were selected and the proton magnetic resonance spectroscopy (1H-MRS) imaging method was used to image the cerebral infarction lesions, the metabolites in the lesions and their clinical value. In the 53 patients who underwent MRS imaging, the NAA concentration in the infarct site was found to be decreased, and the results were consistent with the literature reports. The concentration of Cho was not significantly changed. The typical Lac peak was only found 23 times, and the incidence rate was 43.4%. This may be due to the fact that the concentration of Lac is related to anaerobic metabolism. When the examination time exceeds the acute phase of stroke, the blood vessels around the hypoxic brain tissue revascularize and the oxygen supply increases, so Lac cannot be detected. In addition to this, when the total amount of Lac is small, contamination due to Lipid peak also reduces the detection rate of Lac.

Characteristics of magnetic resonance spectroscopy images of stroke patients complicated with type 2 diabetes

Cerebrovascular disease is a chronic complication of diabetes and one of the leading causes of death in diabetic patients; hyperglycemia is also an independent risk factor for stroke (15–18).

The infarction site of diabetic patients with stroke is common in basal ganglia, corona radiata and brain lobe. The infarct type is mainly small infarct, and can also be found in the thalamus, quadrigemina, lateral ventricle and other parts. In order to reduce the error caused by the different content of metabolites in different measurement sites, the basal ganglia infarct was selected as the measurement site. Comparing the MRS images of the basal ganglia infarction area of the three groups of patients, we found that the NAA/Cr value of the satisfactory glycemic control group was not significantly different from that of the good glycemic control group, while the NAA/Cr value of the poor glycemic control group was significantly lower than that of the good glycemic control group. The Cho/Cr index did not show a significant difference between the three groups. There was no significant difference in the appearance of Lac peak between the three groups. In

TABLE 1 Clinical characteristics of 53 stroke patients.

Indicator (Mean/Range)	Stroke patients (n = 53)		
	Good glycemic control group (Group A)(n = 31)	Satisfactory glycemic control group (Group B)(n = 9)	Poor glycemic control group (Group C)(n = 13)
Sex (Male/Female)	21/10	5/4	7/6
Age (years)[a]	70.2/49–90	71.6/60–84	67.5/46–87
LDL-C (mmol/L)[a]	2.63/1.05–4.61	2.91/1.17–4.89	3.42/1.67–5.44
FBG (mmol/L)[a]	5.16/3.77–6.91	5.90/4.63–7.60	9.29/4.99–16.89
HBA1C (%)[a]	5.8/5.0–6.3	6.8/6.5–7.2	9.7/7.6–13.2

LDL-C, low density cholesterol; FBG, Fasting blood sugar; HBA1C, glycosylated hemoglobin. [a]Median (range).

TABLE 2 NIHSS scores of three groups of patients.

	≤6 points	6∼16 points	≥16 points	Range	Median
Group A (n = 31)	26	3	1	0∼16	2
Group B (n = 9)	7	2	0	0∼9	5
Group C (n = 13)	7	6	0	0∼12	6

NIHSS, National Institutes of Health Stroke Scale; Group A, Good glycemic control group, HbAlc < 6.5%; Group B:Satisfactory glycemic control group, HbAlc: 6.5% 7.5%; Group C: Poor glycemic control group, HbAlc > 7.5%. Range: the highest and lowest of the NIHSS scores of each group of patients; Median: the median NIHSS score of each group.

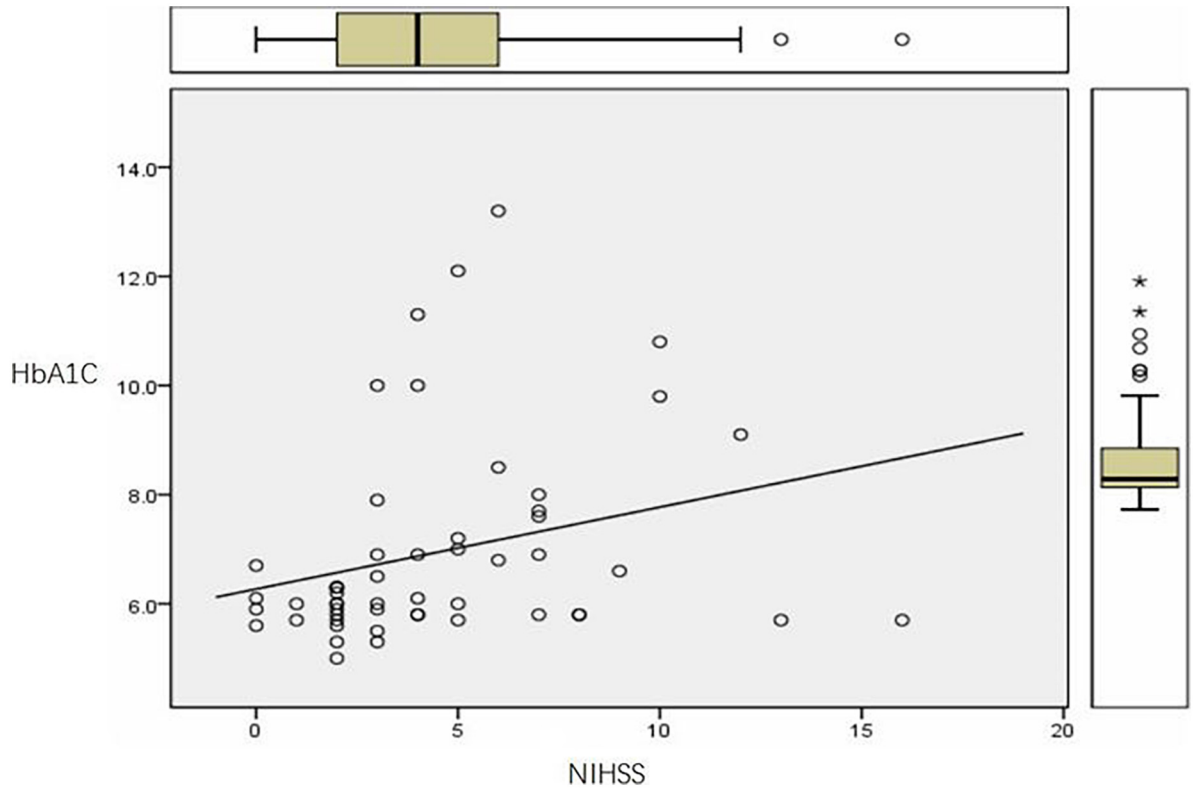

FIGURE 1
HbA1C and NIHSS diagram.

the observed Lac peak, Lac/Cr was significantly higher in the poor glycemic control group as compared to the good glycemic control group, but the correlation was not obvious. This may be related to the small number of observations of the Lac peak and the lower concentration of Lac. At the same time, we also found that even in the area where no infarction occurred, the NAA/Cr

TABLE 3 Characteristics of metabolites following brain infarct for the three groups.

Metabolites $\chi \pm S$	Group A ($n = 31$)			Group B ($n = 9$)			Group C ($n = 13$)		
	IS	MI	*P*-value	IS	MI	*P*-value	IS	MI	*P*-value
NAA/Cr	1.09 ± 0.22	1.67 ± 0.36	0.007**	0.91 ± 0.14	1.16 ± 0.24	0.038*	0.87 ± 0.21	1.16 ± 0.26	0.029*
Cho/Cr	0.87 ± 0.19	1.04 ± 0.38	0.039*	0.79 ± 0.21	1.07 ± 0.41	0.036*	0.74 ± 0.19	1.3 ± 0.40	0.030*
Lac/Cr	0.35 ± 0.10	0	/	0.38 ± 0.13	0	/	0.49 ± 0.12	0	/

Group A, Good glycemic control group, HbAlc < 6.5%; Group B: Satisfactory glycemic control group, HbAlc: 6.5% 7.5%; Group C, Poor glycemic control group, HbAlc > 7.5%; IS: Infarcted area side; MI, Mirror of infarcted area; NAA, N-acetyl aspartate; Cr, Creatine; Cho, Choline; Lac, Lactate.
*$P < 0.05$, **$P < 0.01$.

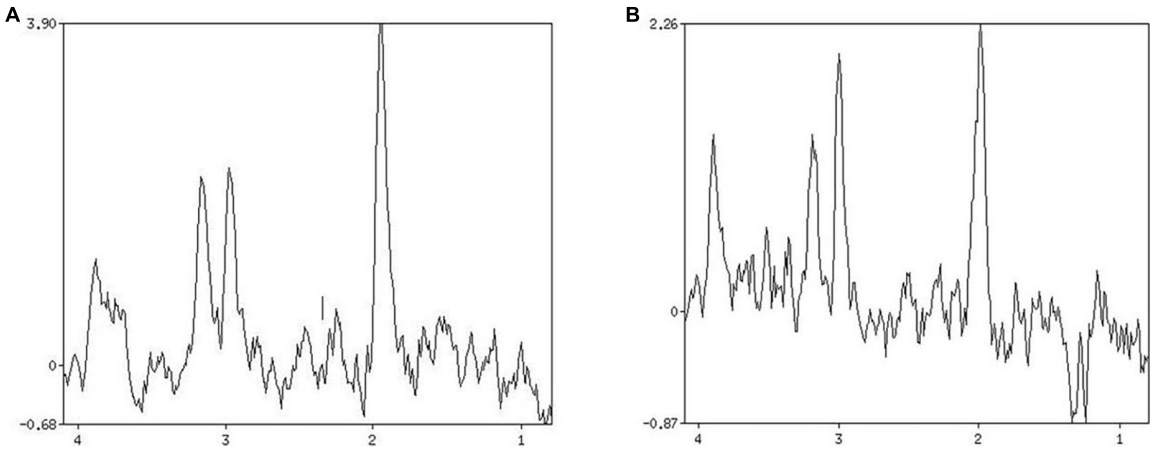

FIGURE 2
Patient 1 HbAlc: 5.7. **(A)** MRS shows changes in brain metabolites in the infarcted area, NAA/Cr 2.334, Cho/Cr 1.332. **(B)** MRS shows changes in brain metabolites in the contralateral side at the same site, NAA/Cr 1.780, Cho/Cr 0.985.

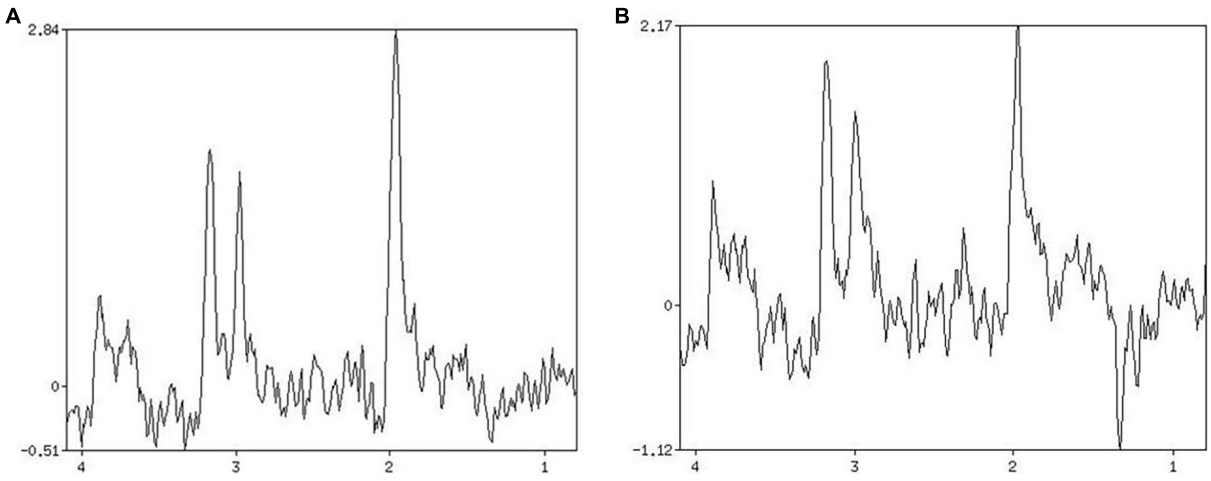

FIGURE 3
Patient 2 HbAlc: 10.3. **(A)** MRS shows changes in brain metabolites in the infarcted area, NAA/Cr 1.906, Cho/Cr 0.926. **(B)** MRS shows changes in brain metabolites in the contralateral side at the same site, NAA/Cr 1.422, Cho/Cr 1.571.

value of the poor glycemic control group was lower than that of the good glycemic control group, which further indicates that the blood sugar elevation aggravates the nerve fiber damage and anaerobic metabolism. Therefore, Stroke patients who are also diabetic often have more severe clinical symptoms and a poorer prognosis.

NAA is a marker of neuronal cell integrity. Our study found that blood HbA1C levels were negatively correlated with NAA/Cr in patients with AIS, i.e., the higher the glycated hemoglobin level, the greater the destruction of neuronal cell integrity. Cho reflects the renewal state of the cell membrane. This experiment found that the level of HbA1C was negatively correlated with Cho/Cr, that is, high levels of HbA1C slowed down cell renewal and decreased cell viability. These results further confirm the fact that an increase in blood glucose causes a decrease in neuronal activity and also causes nerve fiber damage.

The increase in HbA1c leads to an increase in the incidence of stroke, the disease has an increased severity and this may be due to: (1) effects of long-term hyperglycemia, hyperglycemia end products accumulate in the patient, leading to thickening, damage, and stimulation of the inner wall of the blood vessel. The release of inflammatory cytokines promotes the formation of atherosclerosis and cerebral arterial thrombosis, which ultimately induces stroke; (2) hyperglycemia reduces the formation of new blood vessels through the action of low vascular endothelial growth factor, inducing a reduced perfusion in the periphery of the lesions and lactic acid accumulation in the brain also promotes the development of hypoperfusion which causes irreversible infarction and which therefore accelerates the pathological process of the lesion; (3) microvascular dysfunction caused by diabetes, vascular endothelial proliferation, increased blood viscosity, decreased blood flow velocity, red blood cells and platelet aggregation occur which then leads to the formation of thrombus which further increases the incidence and recurrence rate of stroke.

Correlation between magnetic resonance spectroscopy parameters and national institutes of health stroke scale scores

The National Institutes of Health Stroke Scale (NIHSS) is a clinically used scale for assessing neurological deficits in patients with acute stroke. It has become an important part of the clinical evaluation and clinical trial system for acute stroke. The standard NIHSS consists of 15 items, including language, motor function, sensory function, and movement. The score ranges from 0 to 42. A score < 6 points indicate a good prognosis. A score > 16 points indicate the possibility of death and severe disability.

No significant correlation was observed between NIHSS score and NAA/Cr, Cho/Cr, and Lac/Cr detected by MRS in this study. The NIHSS score is a result of clinicians' evaluation of patients, as such it is subjective and cannot completely reflect the neurological impairment of patients. MRS is more sensitive and can detect microscopic changes in substances, but these small change does not necessarily affect the patient's clinical symptoms, that is, "only qualitative changes occur, without quantitative changes occur." We therefore need to question whether these is a threshold for symptomatic change to occur. When the concentration of substances detected by MRS exceeds a certain threshold, this could potentially a greater impact on the NIHSS score, which needs to be studied further. The equations should be inserted in editable format from the equation editor.

Conclusion

Magnetic resonance spectroscopy is the only non-invasive imaging method for studying the metabolism, biochemical changes and for quantitative analysis of compounds in living organs. NAA/Cr, Cho/Cr, and Lac/Cr are quantitative indicators that show the changes in brain chemical metabolism in stroke patients after the onset, providing a direct imaging basis for the severity and prognosis in stroke patients. Elevated blood glucose is an important risk factor for stroke and a major cause of increased mortality among stroke patients. Using MRS imaging method, the damage to the brain caused by hyperglycated hemoglobin is explained from the perspective of microscopic substance changes. This technique helps to better assist in the early clinical diagnosis and prognostic assessment of stroke disease.

The shortcomings of this study are as follows: 1. MRS examination time is too long, the movement of patients with acute stroke will increase the chance of artifacts, the signal is weak, the spatial resolution is poor and its application in acute stroke still requires a better understanding and further improvement; 2. Due to the fact that the sample size is not big enough, the research on the changes in Cho value in infarcted lesion area is therefore not complete. Follow-up studies on this matter will need to expand the sample size and improve the detection of Cho and add additional observation indicators to the study.

Data availability statement

The original contributions presented in this 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 the Ethics Committee of Gongli Hospital of Shanghai Pudong New Area. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YuW, YiW, and GP: conceptualization and writing—original draft preparation. WL and JC: data curation. KC and XY: investigation. JJ: supervision. BH: supervision and writing—review and editing. All authors approved the submitted manuscript.

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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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Using standardized patients to assess the quality of type 2 diabetes care among primary care providers and the health system: Evidence from rural areas of western China

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Background: Improving type 2 diabetes (T2D) care is key to managing and reducing disease burden due to the growing prevalence of diabetes worldwide, but research on this topic, specifically from rural areas, is limited. This study uses standardized patients (SPs) to assess T2D care quality among primary care providers to access the healthcare system in rural China.

Methods: Using multi-stage random sampling, health facilities, providers, and households were selected. SPs were used to evaluate providers' T2D care quality and a questionnaire survey was used to collect patient sorting behaviors from households. Logistic regression was used to explore factors correlated with T2D care quality. Provider referral and treatment rates were combined with patient sorting behaviors to assess the overall quality of T2D management by rural China's healthcare system.

Results: A total of 126 providers, 106 facilities, and 750 households were enrolled into this study. During SP interactions, 20% of rural providers followed the national guidelines for T2D consultation, 32.5% gave correct treatment, and 54.7% provided lifestyle suggestions. Multi-variable regression results showed that providers who had earned practicing certificates (β = 1.56, 95% CI: 0.44, 2.69) and saw more patients (β = 0.77, 95%: 0.25, 1.28) were more likely to use a higher number of recommended questions and perform better examinations, whereas providers who participated in online training were less likely to practice these behaviors (β = −1.03, 95%: −1.95, −0.11). The number of recommended questions and examination (NRQE) was the only significant correlated factor with correct treatment (marginal effect = 0.05, 95%: 0.01, 0.08). Throughout the rural healthcare system, 23.7% of T2D patients were treated correctly.

Conclusion: The quality of T2D care in rural western China, especially throughout the consultation and treatment process during a patient's first visit, is poor. Online training may not improve T2D care quality and low patient volume was likely to indicate poor care quality. Further research is needed to explore interventions for improving T2D care quality in rural China's healthcare system.

KEYWORDS

quality of type 2 diabetes care, standardized patients, healthcare system, rural China, primary care

Introduction

Diabetes is a leading cause of mortality and reduced life expectancy around the world. From 1990 to 2017, the global prevalence of diabetes increased more than 129% from 211 to 476 million, and the number of global deaths due to diabetes increased more than 125% from 0.61 million deaths to 1.37 million (1). Type 2 diabetes (T2D), the most common type of diabetes, accounts for ∼90% of all diabetes cases internationally (2). In response to the major disease burden diabetes presents, organizations worldwide have set forth measures for decreasing diabetes' prevalence. For example, the United Nations Sustainable Development Goals (SDG) included the aim to reduce premature mortality from non-communicable diseases (NCDs), including diabetes, by one-third by 2030 (3). Similarly, the World Health Organization's (WHO) Global Action Plan for the Prevention and Control of NCDs has proposed a series of measures for the surveillance, prevention, and control of diabetes and its complications, as well as specific measures for diagnosing and treating T2D (4).

In 2019, China reported having the largest number of adults with diabetes in the world (116.4 million) and predicted that this number would increase to 147.2 million by 2045 (5). In order to decrease the prevalence and reduce the complications associated with diabetes, China implemented a comprehensive healthcare policy and has established 265 national demonstration areas where short-term pilot programs aim to promote better healthcare practices as well as better detection methods for controlling the prevalence of chronic diseases (6). Additionally, China has further developed healthcare system integration throughout the country to promote the flow of healthcare resources to primary care facilities for long term health programming (7).

Healthcare systems play a foundational role in dealing with the increasingly high prevalence of non-communicable diseases (8), including diabetes. In China, the rural healthcare system is comprised of three tiers of healthcare providers: village clinics (VC), township health centers (THC), and county hospitals (CH). Under China's guidelines for diabetes management within the rural healthcare system, primary care providers from VCs and THCs take primary responsibility in diagnosing patients during their initial visits and treating the diagnosed patients. First-time patients are recommended to visit a VC or THC, and to then visit a CH if their health issues remain unresolved (9). As a result of these healthcare system developments, diabetes prevention and treatment services in China have been gradually transferred from city hospitals to local primary care providers, which has improved diabetes patients' access to diagnosis and treatment (10).

Despite patients' improved accessibility to diabetes healthcare services, the complex phenotypes and multiple needs of individuals with diabetes requires high quality diabetes care and a healthcare system designed to reduce the burden of this NCD (11). However, previous studies on the quality of diabetes care (that analyzed the counseling and examination process quality, the treatment quality, and subsequent health outcomes) have identified suboptimal performance during initial case diagnosis, evidenced by, for example, a lack of essential examinations (12, 13). Furthermore, for T2D in particular, there is little known about the differences in healthcare system quality in regards to a patient's choice of healthcare facility for their first visit (i.e., whether a patient chooses to first visit a VC or a THC). This is particularly relevant given the gaps in T2D care quality between the different tiers of providers. Combined with the increasing burden on primary care providers for managing T2D, understanding the quality of T2D care and how it may vary by a patient's visiting behavior among China's three-tier rural healthcare system is vital to identifying areas for improvement.

One of the fundamental problems with assessing the quality of T2D care is the methodological limitations of previous

Abbreviations: T2D, type 2 diabetes; VC, village clinic; THC, township health center; CH, county hospital; SP, Standardized Patient; NCD, non-communicable disease; LMIC, low- and middle-income country; NRQE, number of recommended and essential questions and examinations; OLS, ordinary least squares; FPG, fasting plasma glucose; HbA1c, hemoglobin A1ce; OGTT, oral glucose tolerance test.

studies; for example, studies that had used electronic medical records or questionnaire survey data on patient care outcomes often found the method to lead to incomplete and inaccurate results (14). Instead, the standardized patients (SPs) method has become considered as the "gold standard" for evaluating the quality of clinical practice (15). SPs are individuals recruited from local communities and trained to present consistent disease cases to healthcare providers. There are three distinct advantages to assessing clinical practice with SPs compared to other commonly used methods (15, 16). First, because providers are unaware they are being assessed during SP interactions, clinician behavior remains unbiased, compared to the direct observation method which has been found to introduce Hawthorne effects to a provider's observed behaviors (16, 17). SPs can also reduce or eliminate recall bias compared to the method of surveying actual patients after a visit. Second, SPs can measure "real" clinical practice as opposed to only measuring clinical knowledge (which is commonly examined using clinical vignettes or a questionnaire survey, leading to providers being aware of being assessed). Third, because the SP approach examines complete interactions between providers and mock patients, the referral process between the different tiers of healthcare facilities may be observed in practice; these observations may then be used to evaluate the quality of the overall healthcare system. The SP approach has been used in China and internationally to investigate how diseases such as diarrhea, unstable angina, and tuberculosis are treated (18–20). However, to our knowledge, few studies have used SPs to evaluate the quality of T2D care, especially in rural China where the prevalence of diabetes increases by 2.5% points annually (21).

In order to fill this identified gap in the literature, the present study has three objectives. First, we use SPs to assess the quality of T2D care among primary healthcare providers in rural China. Second, we explore the correlates of the quality of T2D care and seek to provide policy or healthcare reform implications for improving the quality of T2D care in rural China. Third, we combine patients' facility sorting behaviors and provider-level quality analyses of T2D to determine the ability of China's rural healthcare system for effectively managing diabetes.

Materials and methods

Setting and sampling

The facilities and healthcare providers sampled for this study were selected from rural areas in one prefecture of Sichuan Province in western China. The sample was chosen using a four-stage random sampling procedure. First, five counties were randomly selected from the prefecture. Second, 50 townships were randomly selected from these five sample counties. Third, the sample was then evenly divided with 10 townships chosen from each county. Fourth, one village was randomly selected from each sample township. In total, 50 villages from the sample townships were enrolled into the study. All providers of general and internal medicine who were on duty on our survey day from the sample facilities within the sample villages were surveyed. From this sampling process, a total of 126 providers were included in the study (see Figure 1).

Data collection

Provider survey

Structured questionnaires were administered to collect provider information. Trained investigators interviewed providers to obtain information regarding their age, gender, medical education, qualifications, medical experience, income, and undergraduate major.

Household survey

Residential-level demographics—including household socio-demographic characteristics, whether a member of the household had been diagnosed with diabetes, and the facility-sorting behavior of the household members (i.e., whether they choose to first visit a VC or a THC)—were collected by trained investigators through face-to-face interviews. The choice of which facility a patient visits first is important in evaluating the quality of China's rural healthcare system in diagnosing and treating T2D, as this choice determines how the patient will be diagnosed and initially treated, which subsequent facilities they will visit through referrals, and the efficacy of the treatment process as a whole. Therefore, all households were asked which facility a member would choose to visit first when they experienced symptoms related to diabetes, such as eating more, drinking more, and unexplained weight loss.

Standardized patients

Provider quality was assessed through their interactions with incognito SPs. T2D is a disease that qualifies for being assessed by the SP methodology as (1) there are no obvious physiological symptoms of T2D and (2) there is low risk that SPs will be exposed to invasive procedures or tests during an initial examination. Thus, using SP interactions, we assessed providers' process quality and the accuracy of their diagnosis and treatment. The standards of quality assessment we used were taken from Chinese clinical guidelines (22), which are presented in Appendix Text 1.

SPs were recruited from local communities and selected through interviews with our research team to confirm that their demographic characteristics matched the standardized T2D case profile. All selected SPs were trained in a classroom setting for 1 week by a team of researchers and consulting

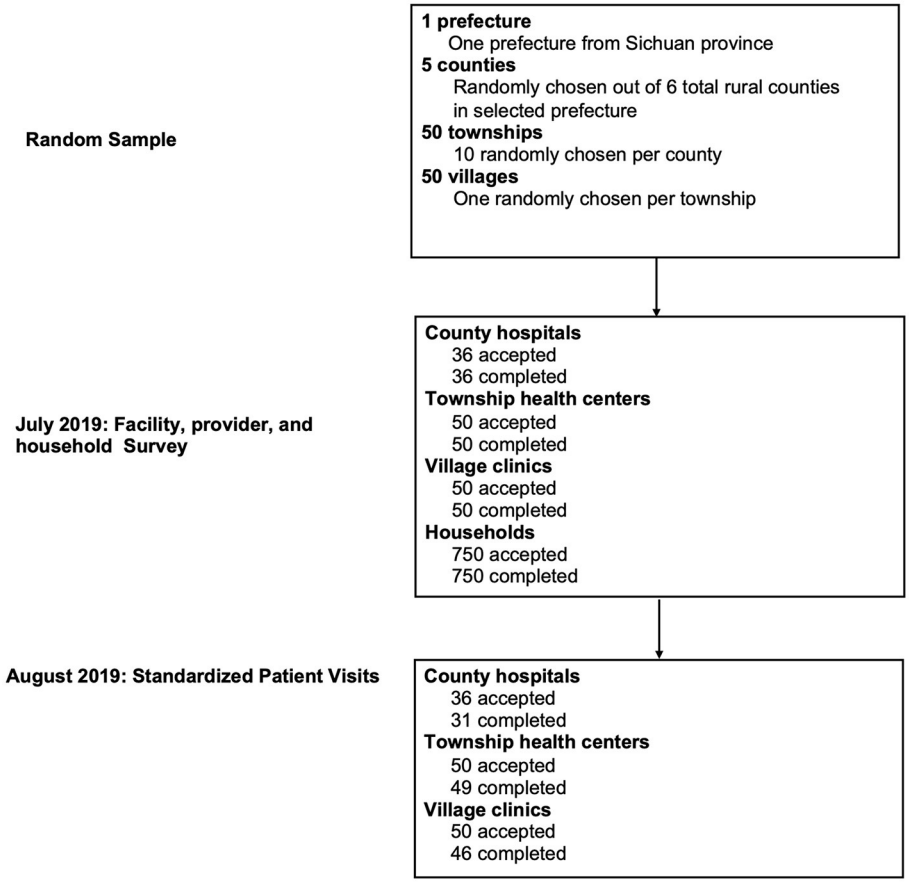

FIGURE 1
STROBE flowchart. Standardized patients were randomly assigned to facilities and within each facility, standardized patients visited the provider following normal procedures for walk-in patients. Fifteen households were randomly selected from the resident roster of each sample village, totaling 750 households.

medical professionals in order to present consistent T2D cases. Classroom training focused on preparing SPs to represent the T2D case to providers in a consistent and unsuspicious manner. Medical professionals discussed the symptoms of T2D to be portrayed by SPs and the typical behavior and presentation of real patients afflicted with the diseases. Following classroom instruction, the SPs went through extensive field rehearsals in rural areas with clinicians who volunteered to assist with the study.

All SPs followed a standardized case script which was developed by our research team in conjunction with diabetes specialists. To adapt the case script to the local context, local diabetes prevention and management authorities were also included in the consultations. The details of the case script can be found in Appendix Text 2. To prevent invasive testing on an SP, such as a Fasting Plasma Glucose test, every SP carried a prepared blood glucose test report form with them for their visit. If a provider asked them to take an invasive examination, the SP would present the test report to them.

SP visits

SPs visited the target providers in late August 2019. One SP visited one provider in each sample facility. Each SP was randomly assigned to a provider to reduce the potential for any differences in individual SP presentations and to reduce bias comparisons across providers. Upon entering each clinic, the SP was seen by any provider who was available at the time. In other words, SPs made no attempt to be seen by specific providers.

We used three methods to collect data on SP-provider interactions. First, SPs wore a concealed recording device. This allowed the research team to accurately evaluate interactions without relying on the SP's ability to recall details. Second, SPs were administered a case-specific "debriefing survey" upon exiting clinics. This survey covered the SP's interaction with the provider, the SP's own impressions of the provider, and any additional observations made by the SP that they thought were relevant but not captured on the audio recording. Finally, to collect information on any drugs dispensed, SPs were directed to purchase all medications prescribed to them by the provider.

Statistical analysis

We calculated the means or proportions across all interactions for each of our primary outcomes: (1) the SP-provider consultation process as determined by the number of recommended questions and examinations (henceforth referred to as NRQE) asked and conducted by the provider; (2) the correct diagnosis as determined by the accuracy and completeness of the provider's diagnosis; and (3) the correct treatment as determined by the overall accuracy of the provider's prescribed treatment. All outcome variables were evaluated according to China's national clinical guidelines (22). To assess the correlates of these variables, we used ordinary least squares (OLS) regression for the NRQE variable (continuous variable) and logistic regression for the correct diagnosis and correct treatment variables (binary variables). For each outcome, we assessed correlations with a fixed set of facility-level and provider-level characteristics hypothesized to be related to T2D care quality.

We simulated system-level results by combining patient sorting behavior data with provider competence data from VCs and THCs to build a T2D management chain that represented the entire rural healthcare system. We used the patient sorting behavior data collected by the household survey to determine which facility a patient would visit first; we then used T2D treatment and referral data at the facility level to determine whether a patient would be treated correctly at that facility or to where the patient would be referred for further treatment. For instance, if a patient initially visited a VC, we used the correct treatment data and referral data at the VC tier (and, subsequently, the THC level) to calculate the probability of diabetes being correctly managed within the rural healthcare system. All analyses were conducted using STATA 14.0 (StataCorp, College Station, TX, USA).

Results

Provider characteristics

Table 1 shows the characteristics of all sampled providers. Out of the total 126 providers who were enrolled into our study, 36.5% (46/126) were from VCs, 24.6% (31/126) were from CHs, and the remainder were from THCs (38.8% or 49/126). VC providers had a lower education level than providers from THCs and CHs ($P < 0.001$). Moreover, VC providers had fewer practicing certificates; only 23.9% of VC providers held a practicing certificate, which was a significantly smaller proportion than providers working in THCs and CHs (91.8 and 96.8%, $P < 0.001$), respectively. During their undergraduate studies, 56.5% of VC majored in western medicine, compared to 79.6 and 77.4% of providers from THCs and CHs, respectively ($P < 0.05$). There were also significant income gaps between providers in the three tiers. The income of THC providers was twice the income of VC providers, and the income of CH providers was three times the income of VC providers ($P < 0.001$). Finally, 80.6% of CH providers had participated in online training, which was a significantly higher proportion than that of THC and VC providers ($P = 0.005$).

Quality of SP-provider interaction process, diagnosis, and treatment

Results on the quality of T2D care among providers in the rural healthcare system are reported in Table 2. On average, providers used six of the 31 recommended questions and examinations (20%); no significant differences were found among the three tiers of providers (all *P*-values more than 0.05). The providers asked an average of 3.3 recommended questions out of the 19 questions required by the national clinical standards for diagnosing T2D, and performed 2.8 of the 13 required examinations. The correct diagnosis rate was more than 90% among providers from THCs and CHs, whereas only 69.6% of VC providers made correct diagnoses ($P < 0.01$). Overall, the correct treatment rate was generally below 40% and did not differ significantly among providers from the three tiers of facilities; however, when it came to prescribing the appropriate drugs, providers from VCs prescribed fewer correct drugs (41.4%) and more harmful drugs (23.9%) to patients than providers from both THCs (78.6 and 4.1%) and CHs (83.3 and 0%; all $P < 0.05$). Regarding non-pharmaceutical treatment plans, about 50% of all providers gave lifestyle suggestions to their patients, and no significant differences were found between providers in all three tiers (all *P*-values > 0.05). Regarding rates of referral, 37% of patients were referred from VCs to higher-tier facilities, whereas only 3.2% of patients were referred from CHs to other facilities ($P < 0.05$).

Turning to the frequency of diagnostic questions asked and examinations performed during SP-provider interactions (Figures 2, 3), more than half of the providers asked the recommended question of whether patients experienced "dry mouth and thirst." Additional recommended questions were about the patient's history of diabetes, if they had previously received blood sugar testing, their age, and any weight changes they experienced in recent months; however, <50% of all providers asked these specific questions to the SPs. Moreover, <20% of all providers asked whether the patient had a family history of diabetes. Nearly all providers conducted capillary blood-postprandial blood glucose tests. Other essential exams were conducted infrequently. About 40% of all providers conducted FPG (Fasting Plasma Glucose) and HbA1c (hemoglobin A1c) tests. Few clinicians (around 5%) conducted the OGTT (Oral Glucose Tolerance Test), a golden standard for T2D diagnosis. Furthermore, although also

TABLE 1 Providers characteristics across three tiers of China's rural healthcare system.

Provider characteristics	VC	THC	CH	*P*-values
Age (SD)	48.1 (7.9)	44.7 (8.4)	49.5 (11.8)	0.055
Gender (1 = male)	34 (73.9%)	32 (65.3%)	15 (48.4%)	0.071
Education (1 = bachelor's degree or higher)	0 (0.0%)	7 (14.3%)	11 (35.5%)	<0.001
Practicing certificate (1 = yes)	11 (23.9%)	45 (91.8%)	30 (96.8%)	<0.001
Major (1 = western medicine)	26 (56.5%)	39 (79.6%)	24 (77.4%)	0.030
Income (Yuan)	2,358.3 (995.9)	4,563.1 (1,352.9)	7,151.6 (3,277.1)	<0.001
Diabetes patients in past 2 weeks (numbers)	5.2 (6.5)	6.3 (5.7)	26.6 (41.5)	<0.001
Diabetes training 1 time per month or more (1 = yes)	11 (23.9%)	7 (14.3%)	6 (19.4%)	0.49
Online training (1 = yes)	20 (43.5%)	27 (55.1%)	25 (80.6%)	0.005
Sample size	46	49	31	

Source: Author's survey.
VC, Village Clinic; THC, Township Health Center; CH, County Hospital; SD, Standard deviation.

TABLE 2 Quality of type 2 diabetes care among providers from China's rural healthcare system.

Diabetes care quality	VC	THC	CH	*P*-values
Process quality				
Number of recommended questions	3.0 (2.0)	3.5 (1.7)	3.3 (1.8)	0.43
Number of recommended examinations	2.5 (1.0)	2.9 (1.1)	2.9 (1.2)	0.13
Number of recommended questions and examinations (NRQE)	5.5 (2.5)	6.4 (2.2)	6.3 (2.3)	0.15
Average percent of recommended questions and examinations (ANRQE)	19.7% (6.2%)	20.2% (7.0%)	19.6% (7.1%)	0.91
Diagnosis quality				
Correct diagnosis	32 (69.6%)	44 (93.6%)	28 (93.3%)	0.002
Treatment quality				
Correct treatment	13 (28.3%)	18 (36.7%)	10 (32.3%)	0.68
Number of drugs dispensed (if any)	2.0 (1.1)	1.6 (1.2)	1.2 (0.4)	0.24
Correct drugs (if any)	12 (41.4%)	11 (78.6%)	5 (83.3%)	0.027
Harmful drugs (if any)	11 (23.9%)	2 (4.1%)	0 (0.0%)	<0.001
Lifestyle guidance (if any)	24 (52.2%)	31 (63.3%)	14 (45.2%)	0.26
Monitoring blood glucose (if any)	19 (41.3%)	31 (63.3%)	20 (64.5%)	0.051
Referral	17 (37.0%)	7 (14.2.0%)	1 (3.2%)	0.017
Sample size	46	49	31	

Source: Author's survey.
VC, Village Clinic; THC, Township Health Center; CH, County Hospital.

considered essential for diagnosing T2D, no THC providers conducted the BMI exam, and very few providers (<5%) from VCs and CHs measured the weight and height of the SPs.

Correlates of T2D care quality

Figure 4 presents the results of the multivariate analysis assessing the correlates for provider process quality. Older providers used 1.14 fewer NRQE than younger providers, while providers with practicing certificates used 1.56 more NRQE than those without practicing certificates. Providers who had more patient visits in the past 2 weeks conducted 0.77 more NRQE. However, providers who had higher incomes addressed 0.35 fewer NRQE than those with lower incomes. Furthermore, providers who participated in online training in the past year conducted 1.03 fewer NRQE than those who did not participate in online training.

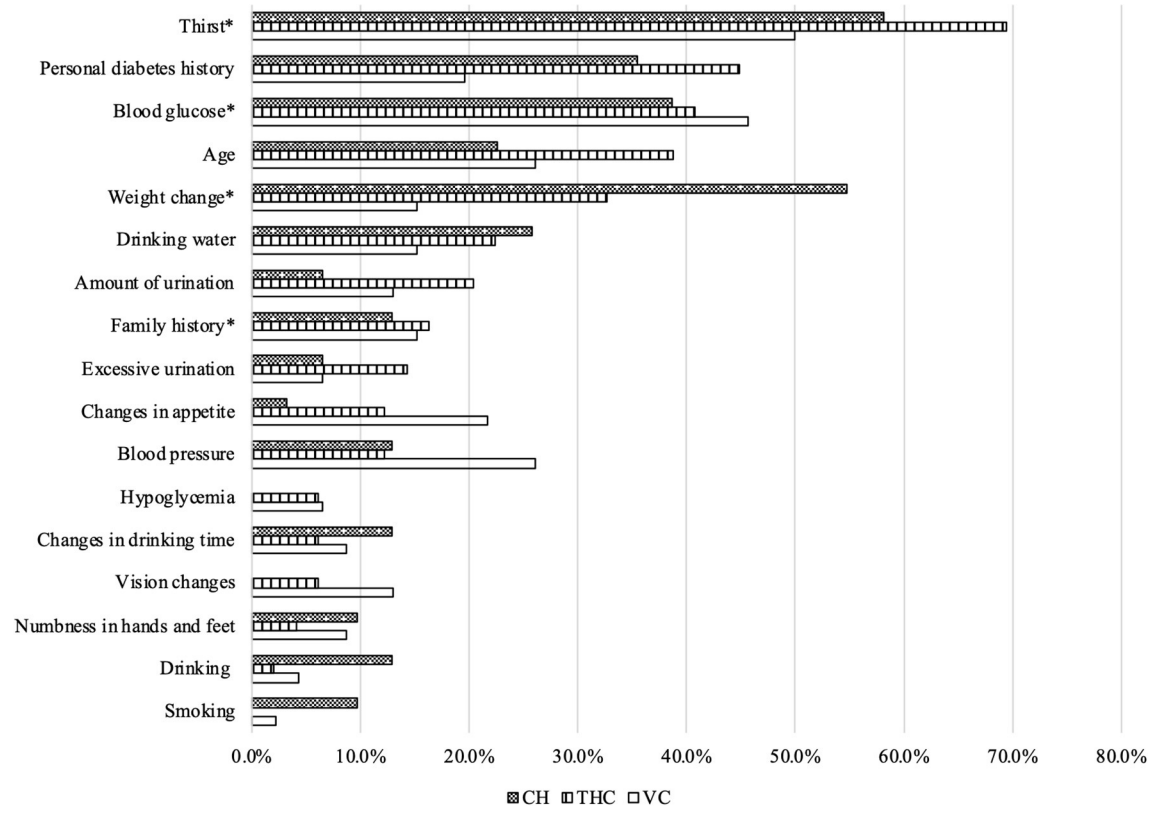

FIGURE 2
Recommended questions used during standardized patient-provider interactions. Source: Author's survey. CH, County Hospital; THC, Township Health Center; VC, Village Clinic; *Essential questions.

Appendix Figure 1 shows the correlates for correct diagnosis among providers. More NRQE addressed during SP-provider interactions was correlated with a higher probability of correct diagnosis by the provider. Similar to the correlates of process quality mentioned above, holding a provider's certificate was positively correlated with a provider's correct diagnosis rate, whereas a provider's income was negatively correlated with their correct diagnosis rate. Regarding the rate of correct treatment (Appendix Figure 2), NRQE was the only significant correlate: Providers who conducted 1 additional NRQE were 5% points more likely to offer correct treatment.

Quality of the healthcare system in managing T2D

To examine the system-level quality of T2D care, we combined provider T2D care quality, referral rates, and patient sorting behavior to generate a model that displayed the treatment of diabetes at each facility and any subsequent patient referral to higher-level facilities under the rural healthcare system (Figure 5). From our collected data on patient sorting behavior, we found that 39% of T2D patients first visited a VC, while 32% first visited a THC, and 29% went directly to a CH. Using the data from Table 2, we attributed correct treatment rates of 28.3% for VCs, 36.7% for THCs, and 32.3% for CHs. Among the patients whose symptoms were not treated at a VC, 15.2% were given a referral to a THC, and 21.7% were referred to a CH directly. Among the 15.2% of patients who transferred to a THC from a VC, 2.2% were subsequently referred to a CH. For patients who visited a THC initially, 14.3% were referred to a CH. Using this model, we were able to calculate the probability that an average rural diabetes patient will receive the correct treatment under the rural healthcare system; this probability came out at 23.7%. Detailed information on the calculation can be found in Appendix Table 2.

Discussion

To the best of our knowledge, this is the first study to evaluate the quality of T2D care using the SP method in rural China. Overall, findings from this study indicate poor

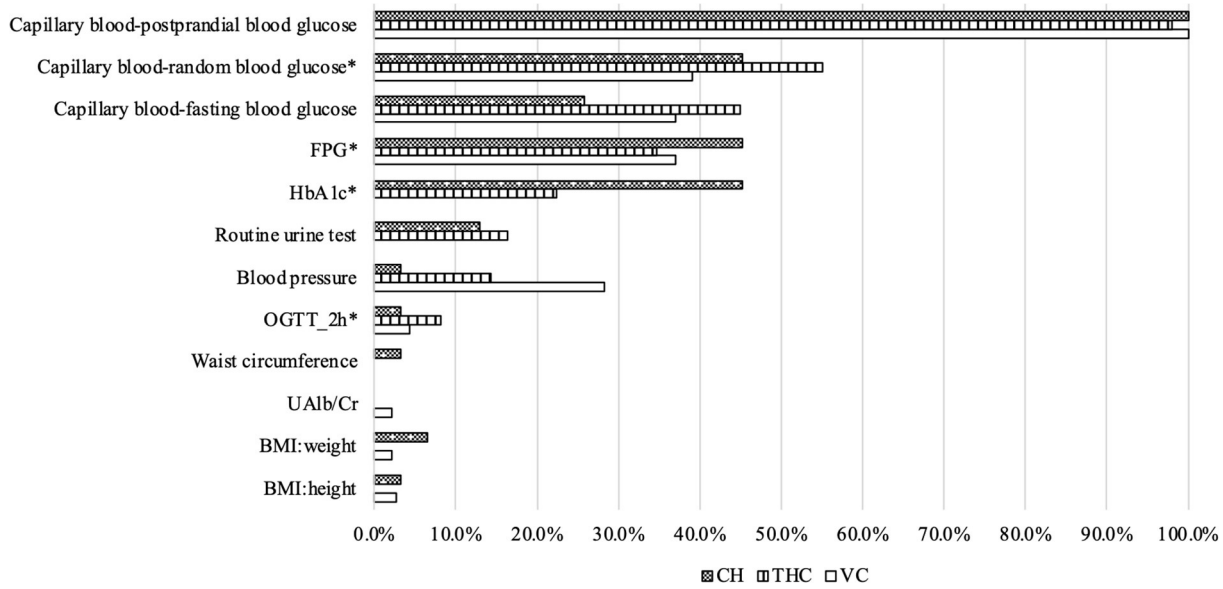

FIGURE 3
Recommended examinations used during standardized patient-provider interactions. Source: Author's survey. CH, County Hospital; THC, Township Health Center; VC, Village Clinic; *Essential examinations.

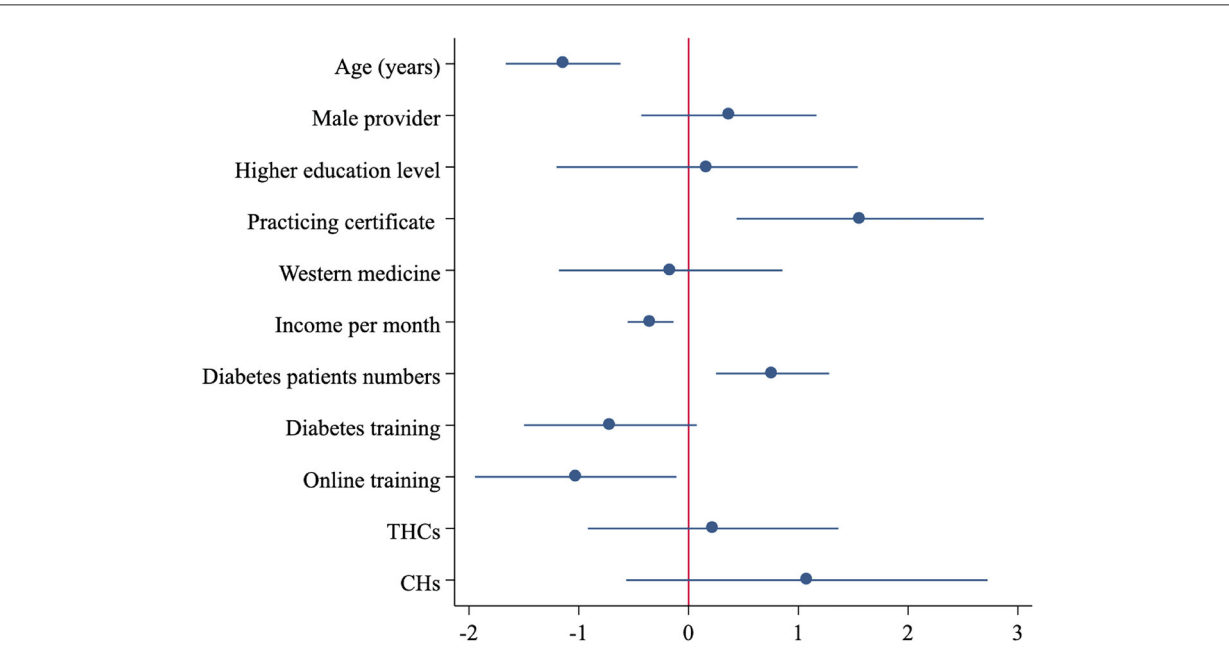

FIGURE 4
Associated factors for correct treatment of type 2 diabetes among rural clinicians. Source: Author's survey. NRQE, number of recommended questions and examinations; CH, County Hospital; THC, Township Health Center.

healthcare quality among rural healthcare providers in China. Regarding the quality of the diagnostic process, on average, less than a third of the recommended diagnostic examinations and questions for T2D were used during the interactions between SPs and providers. Most rural providers correctly diagnosed T2D; however, there existed large gaps in the correct diagnosis rate

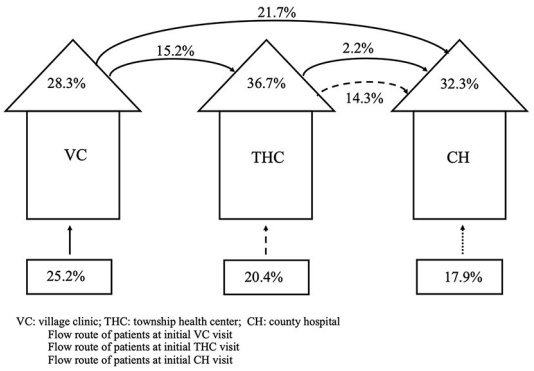

FIGURE 5
Quality of the rural healthcare system assessed through its ability to correctly treat type 2 diabetes. Source: Author's survey. VC, Village Clinic; THC, Township Health Center; CH, County Hospital.

between providers in VCs (who correctly diagnosed 69.6% of SP cases) and providers in THCs and CHs (who gave correct diagnoses in almost 100% of cases). Additionally, despite these differences in correct diagnosis rates, the differences between the providers' treatment plans were small. Moreover, a provider's age, their income, whether they had a practicing certificate, their patient volume, and their level of training were all correlated with their diagnostic process quality, while the diagnostic process quality was the main significant correlate for the quality of diagnosis and treatment of T2D. Finally, when we assessed the overall quality of the rural healthcare system, we identified that the quality of correct treatment prescribed for a T2D patient was <30%.

Due to different quality assessment methods and quality indicators used, our results cannot be directly compared with the results of other studies. For example, one study from rural Uganda used both medical records and patient interview methods to evaluate the quality of the healthcare system, the process of case management (medical examinations in medical records), and patients' health outcomes (13). Another study from Italy employed a continuous *Q*-score to evaluate the quality of healthcare (23). Although we cannot compare our results directly to these studies, we note that two studies from China and Switzerland, using different indicators for quality of care, found overall low quality in the case management process of T2D, which is consistent with our results (24, 25). In addition, using SPs in this study allowed us to record all patient-provider interactions as well as to observe real diagnostic questions asked by providers. Our study found that two essential questions for diagnosing diabetes, specifically questions regarding weight changes and if there was a family history of diabetes, were not frequently asked by providers during the SP interactions, especially by providers from VCs and THCs. We believe that this finding may be helpful when designing interventions for improving the process quality of diagnosing and treating T2D for providers in China's rural healthcare system.

Surprisingly, we found that both process and treatment quality had no statistical difference among the three levels of providers, which was not consistent with previous research. The reason for this may be 2-fold. First, the national policy of "strengthening primary healthcare" with core responsibilities in preventing and managing chronic diseases might have improved the quality of primary healthcare for providers from VCs and THCs (26). Second, we used the SP method to assess the provider's actual clinical behaviors of T2D care instead of assessing their clinical knowledge, which was the measure most frequently used by previous research (13, 27). Additionally, although a knowledge gap may exist between providers from different tiers, clinical behaviors may not change when clinical knowledge increases (28). Therefore, the knowledge-to-real practice gap may be an important reason behind the non-significant difference observed among the three levels of providers, and should be taken into consideration in further quality improvement research.

Our results also showed that providers who had earned a practicing certificate were the ones most strongly correlated with providing better diagnosis process quality, which is consistent with results from previous diabetes healthcare research (29) and from healthcare quality evaluations done in rural China (19). However, some discrepancies with the existing research exist. In one notable example, contrary to findings from Hong Kong primary care settings, where higher patient volume was found to hamper the quality of diabetes care (30), our study's results indicated that higher patient volume was positively correlated with diagnosis process quality. This finding is consistent with evidence from a worldwide systematic review and meta-analysis (31). We believe that a potential reason for this discrepancy may be due to the fact that in Hong Kong, clinics with lower patient volume often have better continuity of care, and thus offer better care for patients with diabetes (30, 32). However, in our study, patient volume was evaluated on the provider level, not on the institutional level. Additionally, prior research has indicated that local providers are more likely to be visited by rural residents in China for primary care than doctors in large hospitals (33). Due to this, we believe that providers with higher volumes of diabetes patients (resulting from higher patient volume in general) are more likely to diagnose and treat diabetes effectively, as they are more likely to develop experience-based expertise for the diseases they frequently see and treat (34). This finding thus leads us to make the suggestion that quality-control measures, such as disease-specific clinical training, should be provided to and emphasized for rural clinicians experiencing less patient volume.

Regarding negatively-correlated factors, a provider's age was negatively associated with the NRQE used during interactions, which is in agreement with results from past studies (35). We

also found that providers who participated in online training were less likely to conduct more NRQE. This is an interesting finding as, in the era of the COVID-19 pandemic, online training has become more widely accepted (36). Despite the growing acceptance of online training, however, our study provides support that more conscious efforts should be made for improving online training programs given to healthcare providers in rural China. We also believe that more research is needed to examine the effects of online training on T2D care quality.

In addition to analyzing the quality of T2D care on an individual healthcare provider level, we also evaluated the quality of T2D treatment among the whole rural healthcare system. Only 38.9% of T2D patients were treated correctly through the rural healthcare system, which is lower than the rate found in previous research assessing rural China's healthcare system's ability to manage tuberculosis (20). Additionally, T2D treatment quality across all tiers was generally low. Even treatment at the CH level, which has always been considered the highest tier of the rural healthcare system, was of lower quality than the treatment provided at THCs, the second-tier healthcare facility that connects VCs and CHs. In light of this finding, we believe that although the policy of "strengthening primary healthcare" reinforced by the Healthy China 2030 Plan announced in 2016 might have improved the quality of primary healthcare in rural areas to a certain extent (37), considering the random patient sorting behavior observed in this study, health policy should not only focus on the quality of primary healthcare, but also focus on an integrated, cooperative primary healthcare system, which fully supports health providers to improve performance (38). A team-based clinical practice intervention (i.e., integrating CHs, THCs, and VCs) and more T2D-specific treatment training for the three tiers of providers may be better ways for improving quality of T2D care and managing T2D in China's rural areas. Finally, our system-level evaluation presented a novel perspective of T2D treatment quality, which we believe could provide ex-ante estimates of the healthcare system for other non-communicable or communicable diseases.

Limitations

Because our research is a part of the project of "Evaluating the Quality of Primary Care for the Early Diagnosis and Treatment of Non-Communicable Diseases in China's Rural Health System," we did not employ a specific sample size calculation. Due to this study's sample size, even though we could identify the quality of care from rural providers and the rural healthcare system in China overall, we were limited to exploring a narrow range of potential contributing factors. Additionally, because the standardized script used was developed for and used by SP volunteers to present the same background and symptoms to providers, this study was unable to measure real patient characteristics. Finally, during SP interactions, all providers' clinical behaviors were assessed in a condition with unknown patients. However, we admit that this method may be limited in an acquaintance society where providers, such as village providers, live in the same rural community as patients and are thus very familiar with their patients.

Conclusion

The quality of T2D care is poor in the rural areas of western China, especially when it came to the quality of the diagnostic process and treatment of T2D during a patient's first visit. Online training may not help to improve clinicians' quality of care for T2D. Moreover, a provider with lower patient volume may indicate that the provider will provide lower-quality care. Further research is needed to explore the causal relation. In addition, our research identified low quality of T2D care observed across the entire rural healthcare system. Finally, our research provided evidence that the rural healthcare system in western China is unable to effectively manage T2D, which may exacerbate the disease burden of T2D and lead to the development of more serious health problems when T2D is improperly treated. Further research is needed to explore potential interventions aiming at improving the T2D quality of the rural healthcare system in China and in other low-income countries.

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 Medical Research Ethics Committee of Sichuan University, China (Registration No. K2019021). The patients/participants provided their written informed consent to participate in this study.

Author contributions

HZ, SS, and SR: conceptualization. YW and RY: formal analysis. HZ and SS: funding acquisition. YW, HZ, CS, SM, ZC, LL, and SS: methodology. YW, HZ, and SR: writing—original draft. YW, RY, CS, SM, ZC, LL, SS, LP, HZ, and SR: writing—review and editing. All authors contributed to the development of the manuscript.

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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.2022.1081239/full#supplementary-material

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Assessment of type 2 diabetes mellitus patients' behavioral characteristics associated with integrated treatment and prevention services in community health centers in China

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Objective: The purpose of this study was to describe behavioral characteristics of type 2 diabetes mellitus (T2DM) patients, identify homogeneous clusters, and explore factors affecting behaviors associated with integrated treatment and prevention (ITP) services for T2DM in community health centers in China.

Methods: A convenient sampling method was employed at a community health center between January and July 2022 in Nanjing. A total of 354 patients completed the self-reported questionnaires. After performing a Cluster Analysis to create a profile of participants' behaviors, a multiple linear regression analysis was conducted to explore the correlations between T2DM patients' characteristics and their behaviors associated with ITP services.

Results: 316 T2DM patients with a mean age of 72.09 years (SD = 5.96) were included. The behavior profiles of patients associated with ITP services were clustered into "Lower" (n = 198) and "Higher" (n = 118) groups, with average scores of 54.41 and 71.46, respectively. Of all the behaviors, complication examination and public health utilization scored the lowest. Health insurance, duration of disease, and treatment modality were independent predictors on the patients' behaviors associated with ITP services for T2DM.

Conclusion: Patients' behaviors associated with ITP services for T2DM were moderately good (the score rate was 63.98%). Of all the behaviors, complication examination and public health service utilization scored the lowest and, as such, may warrant further research. The clustering of patients' behaviors tends to be polarization, distributed at the upper and lower ends of the behavior spectrum. It is necessary to develop and implement targeted interventions for different groups to improve T2DM patients' behaviors associated with ITP services.

KEYWORDS

integrated treatment and prevention, behavior, cluster analysis, multiple linear regression analysis, type 2 diabetes mellitus

1. Introduction

1.1. Prevalence of diabetes in China

The incidence and prevalence of diabetes and its complications are increasing at an alarming rate year upon year, and in turn seriously reducing patients' quality of life (1). Globally, the number of patients with diabetes is expected to rise to 642.80 million by 2030 (2). In 2019, global prevalence, number of deaths in the population, and disability-adjusted life-years (DALYs) in the population associated with diabetes were 6.18%, 1.55 and 70.88 million, respectively (3). The prevalence of diabetes in high-income countries was 8.4% in 2021. The largest prevalence of diabetes was found in upper-middle and middle-income countries, where more than 10% of the population have the condition (4, 5). The International Diabetes Federation (IDF) Diabetes ATLAS (6) indicates that China is the country with the largest number of patients with diabetes in the world. The prevalence of diabetes in China reached 11.2 percent in 2020 (7). The total diabetes-related health expenditure of China in 2021 among adults aged 20–79 years was the second highest in the world, at 165.3 billion USD. The Global Burden of Disease (GBD) (8) suggests that the annual growth rate of DALYs per 100,000 people in China was 2.27% from 1990 to 2019. Diabetes has therefore become one of the major public health problems affecting the Chinese population. Accordingly, addressing the formidable challenge posed by diabetes is a pressing concern.

1.2. ITP services of community health centers in China

China's health care delivery system is highly fragmented (9). In China, medical treatment services are mainly provided by general hospitals, while public health services are mainly provided by community health institutions and centers for disease prevention and control (CDC). These health institutions are often separate and unconnected. Multiple problems arise from the fragmentation of prevention and treatment of type 2 diabetes mellitus (T2DM) in China's health service system (10, 11). For example, it may prevent T2DM patients from accessing continuous health management services, such as health education, disease screening, treatment, and follow-up (12). To further promote the reform of the health system and consolidate the effects of chronic disease prevention and control, "the Medium-to-Long Term Plan of China for the Prevention and Treatment of Chronic Diseases (2017–2025)" proposes (13) to strengthen treatment and prevention collaboration, and promote the integrated development of chronic disease prevention, treatment, and management. Since 2018, the China National Health Commission has made reference to the concept of "Integrated treatment and prevention (ITP) services" in a number of documents. Although there is no specific definition of ITP services, it can be characterized, much like integrated care, as a coherent, coordinated collection of services that can be provided to patients through a variety of organizations, professionals and caregivers (14). Studies have demonstrated that combining prevention and treatment services for T2DM patients not only connects different levels of healthcare to offer patients integrated services that increase service delivery efficiency, but also has a positive impact on patients' blood glucose levels (15).

ITP services of T2DM aim to provide a full range of health services with an emphasis on integrity, coordination, and continuity (16). The quality of integrated services to some extent, can be reflected by the behavioral characteristics of patients with T2DM being treated in community health centers. To date, however, the availability of quantitative evidence on the behavioral characteristics associated with ITP services for T2DM in community health centers in China has been limited. The patients' behaviors associated with ITP services in this study were defined as the activity performances of people with T2DM from various backgrounds in terms of self-control in disease treatment and prevention. Profiling patients' behavior associated with ITP services can be helpful in terms of determining the self-management performance of people with T2DM, and can also represent how the ITP services are evolving. Understanding T2DM patients' typical behavior patterns associated with ITP services and the influencing factors can provide an accurate and objective theoretical and empirical basis for future research.

2. Methods

2.1. Study design and settings

The cross-sectional survey was conducted from January to July of 2022 in Nanjing, Jiangsu Province, China. A community health center was selected from Jiangning District as the sample institution.

2.2. The inclusion and exclusion criteria

2.2.1. Inclusion criteria

(a) Those diagnosed with T2DM, who met the diagnostic criteria of diabetes proposed in China's Guidelines for the Prevention and Treatment of Type 2 Diabetes (2020 edition), (b) Permanent residents of the community (living in the community for more than half a year), (c) Those registered at the community health service center and a contract for diabetes management in the community, (d) Those of sound mind, with effective coordination, and communication skills, (e) Those who volunteered to participate in the research.

2.2.2. Exclusion criteria

(a) Those diagnosed with other types of diabetes, such as type 1 diabetes, gestational diabetes, etc., (b) Those stricken with acute complications such as infection, ketoacidosis, hyperosmolar hyperglycemia, etc., (c) Those suffering from malignant diseases or in the advanced stage of other serious diseases, (d) Those suffering from serious complications of diabetes, such as diabetic nephropathy, fundus lesions, diabetic foot, etc., (e) Those incapable of caring for themselves due to mental illnesses or severe cognitive dysfunction, (f) Those with underlying severe hearing disorders and/or speech impairments.

2.3. Data collection

According to the literature, convenience sampling can be used to draw generalizations about certain sample features and is an option for researchers who are short on time, labor, etc.

Therefore, this method was adopted because of its advantages in affordability, convenience, availability of research objects and applicability of research purposes. Comrey (17) contends that the sample size for general analysis is typically no <200, besides, Tinsly (18) believes that the sample size required by the research should take into account the number of variables in the study. The minimum sample size in the study of exploring influencing factors of related variables was 5–10 times the number of variables (16). As the ITP subscale has 19 items, a minimum sample size of 209 was required with a ratio of 10:1, given 10% of invalid questionnaires. A total of 354 T2DM patients ($N = 354$) were selected for this investigation by convenient sampling methods based on geographic proximity, availability and willingness to participate, and accessibility to the researchers. Due to questionnaire data loss, withdrawal, or duplicate data, 38 patients were eliminated from the investigation, and 316 questionnaires ($n = 316$) were finally included in the study, with the participants response rate of 89.27%. Data collection was carried out by trained investigators of the team according to relevant regulations and respondents were invited to complete face-to-face questionnaires containing demographic information as well as a subscale of behaviors associated with ITP services.

2.4. Measures

2.4.1. The operational definition of ITP

The patients' behaviors associated with ITP services was mainly evaluated in seven dimensions, including dietary control, physical exercise, foot care, medication compliance, glucose and blood pressure monitoring, complication screening, and public health service utilization. The specific measurement items of each dimension were shown in the Supplementary material.

2.4.2. DSKAB-SF

The brief version of Diabetes Self-management Knowledge, Attitude, and Behavior Assessment Scale (DSKAB-SF) consists of three subscales of knowledge, attitude and behavior, with a total of 42 items and a full score of 144, which can achieve the efficient evaluation of diabetic patients in daily health services (19, 20). The knowledge subscale has 22 items and 6 dimensions (basic knowledge, diet, exercise, medicine, glucose and blood pressure monitoring and hypoglycemia prevention). Each item is divided into three levels of "correct", "unclear" and "wrong" and assigned 2, 1, and 0 points in turn, with a full score of 44. The attitude subscale consists of 5 dimensions (attitude of management, diet, exercise, medication, glucose and blood pressure monitoring) and 5 items. The options of "very important", "important", "general", "unimportant" and "very unimportant" are each given 5, 4, 3, 2 or 1 points, for a total of 25. The behavioral subscale is comprised of 15 items with the items as "never", "rarely", "sometimes", "often" and "always", which are successively assigned as 1, 2, 3, 4, and 5 points, with a maximum score of 75. The 6 dimensions of the behavioral subscale are diet, exercise, prescribed medication, foot care, glucose and blood pressure monitoring and complication examination. The higher the score, the better the self-management knowledge, attitude and behavior of diabetic patients. The DSKAB-SF is rapid and thorough in its appraisal of groups or individuals' self-management of diabetes and has strong surface validity and content validity. Therefore, we adopted this brief scale in view of its advantages in good performance, high evaluation efficiency and cultural adaptability (21).

2.4.3. Final questionnaire

On the basis of DSKAB-SF, we added items related to public health of diabetes with reference to the National Basic Public Health Services Standards (third edition) and the National Guidelines for the Prevention and Control of Diabetes in Primary Care (16) to develop the final questionnaire for the survey. The behavior subscale consists of 19 items and the responses range from 19 to 95 based on a 5-point Likert scale (1 = "never", 5 = "always"), a higher result indicating healthier or more desirable behavior. The behavior subscale's Cronbach alpha in this study was 0.84. The behavior of patients associated with ITP services was graded using scoring indices (Table 3). Score index was calculated as follows: (*actual score/the highest potential score*) × 100%, a scoring of <40% is considered poor, a score of 40% to 80% was regarded moderately good, and a score of more than 80% was considered excellent (22).

2.5. Ethical Statement

The study was approved by the Research Ethics Committee of Nanjing Medical University, Nanjing, China and informed consent was obtained from all participants ahead of time (Approval no. 941).

2.6. Data analysis

IBM SPSS 26.0 (SPSS, Inc., Chicago, IL, USA) and R × 64 3.6.3 were used. The behavioral characteristics of all participants were determined applying K-means cluster analysis in accordance with the scores of each dimension in the behavior subscale. The elbow method was first used in the clustering application to determine the ideal number of clusters, followed by the NbClust function, which provides 26 different metrics, and was used to verify the optimal number of clusters. A R package fpc was then used, measuring the similarity between objects in the dataset by silhouette coefficient, to evaluate the quality of clustering. Finally, the fviz cluster function of factoextra package was used to visualize the clustering findings.

Sociodemographic factors and clinical information were the explanatory variables, and patients' behaviors associated with ITP services were the outcome variables in this study. Pearson's correlation test was used to analyze the correlation between independent variables and patients' behaviors, and multiple linear regression was conducted to present the results. Dichotomous "dummy variables" generated from the multi-categorical variables were added to the stepwise regression analysis along with the continuous variables. The Durbin-Watson statistic was computed for the independence test in the analysis, and residual histograms were shown to test for normality. In additions, we stipulated the regression models with

variance inflation factors (VIF) <3 to satisfy the assumption of multicollinearity.

3. Results

3.1. Basic characteristics

The average age of the participants in this study was 72.09 ± 5.96 years, of whom 74.05% were female. The average disease course was 10.54 ± 7.32 years. 47.78% of patients were overweight. 42.09% of the patients were illiterate and 33.23% had primary education. Most patients were married or cohabiting (74.05%), unemployed (93.99%), and on a low-income (96.20%). 14.87% did not have any insurance. The majority of patients had no family history of diabetes (68.04%), but had a history of hospitalization (62.66%) and nearly half of the patients had complications of diabetes (46.52%) (Table 1).

3.2. Behavioral characteristics

In this paper, the k-mean algorithm was used for cluster analysis with patients' behavior scores of each dimension as input variables. We calculated the Within Sum of Squares (WSS) in the cluster for each k value. WSS curve was drawn according to cluster number k, and position of the inflection point (elbow) in the curve was generally regarded as an indicator of the appropriate cluster number. It can be seen the inflection point of the curve was roughly around 3 from Figure 1. Figure 2 shows that the number of indicators supporting 2 clusters is the largest. Therefore, it can be determined that the number of clusters in k-means clustering is 2. The silhouette coefficient is an evaluation index of cluster density and dispersion, and the silhouette coefficient of the clustering result in this study is 0.44 illustrating the result of sample clustering is comparatively reasonable. The scores across 7 dimensions were used as variables for cluster analysis, and the Euclidean method was used to measure the distance of the dissimilarity matrix. The obtained visual clustering results are shown in Figure 3.

The behavior subscale was used to measure the degree of patients' behavior associated with ITP services in the process of health management of T2DM, and its mean value was 60.78 (SD = 10.92, range 19–95). The patients' behavior with the highest score rate was medication compliance (score rate was 93.00%), and the patients' behavior with the lowest score rate was complication examination (score rate was 40.40%) (Table 2). The average score of patients' behavior in 198 T2DM patients in the "Low" group was 54.41 ± 6.32, among which 197 patients recorded moderately good behavioral performance, accounting for 99.49%. The mean score of patients' behavior in the "High" group was 71.46 ± 8.35. Within this group, 30 patients (33.68%) recorded excellent performance associated with ITP services, whilst 88 patients (66.32%) recorded moderately good performance (Table 3).

The mean values of each dimension of patients' behaviors associated with ITP services in the two categories are shown in Table 2. *T*-test was performed on the scores of the two subgroups, which showed that the distribution differences of each dimension between the two groups were statistically significant ($P < 0.001$).

3.3. Association between basic characteristics and patients' behaviors

The differences in health insurance ($\chi^2 = 95.198$, $P < 0.001$), disease course ($t = 2.366$, $P < 0.05$), and treatment strategies ($\chi^2 = 7.611$, $P < 0.05$) between cluster 1 and cluster 2 were statistically significant (Table 1). Among the "High" group, the average duration of diabetes was longer (11.85 ± 7.95). There was also a greater number of uninsured individuals (38.14%) and higher incidence of insulin use (60.17%) than among the "Low" group (Table 1).

A correlation matrix of variables in Table 4 showed significant differences in patients' behaviors among health insurance, DC, and TS ($p < 0.05$). Table 5 showed the results of the multiple linear regression analysis with insurance, DC, and TS as independent variables, and patients' behaviors as dependent variables. The final model of the stepwise regression incorporates three factors (UEBMI, URRBMI, and combination therapy). The regression equation established was $\hat{Y} = 72.765 - 18.095X1 - 15.085X2 + 5.980X3$, $R^2 = 0.294$, which suggests that the independent variables included in the regression model explain 29.4% of the ITP behaviors. The regression model was statistically significant ($F = 43.308$, $p < 0.001$).

4. Discussion

This study focused on typical patients' behaviors associated with ITP services among T2DM patients, and provides quantitative evidence available for reference to further explore the factors and mechanisms influencing ITP services in T2DM prevention and control. There are a limited number of clustering technology studies on the behavior of T2DM patients. The majority of the current studies concentrate on identifying profiles of lifestyle behaviors or self-management behaviors of T2DM patients, and exploring the influencing factors and their relationship with health outcomes (23–27). It is of great significance to identify typical behavioral patterns in T2DM patients.

The sample included in this study was primarily made up of older people with T2DM who were from low-income, low-educated, marginalized groups. As shown in Table 1, 133 (42.09%) of the participants were illiterate, 93.99% were retired, and 96.20% had a monthly income of <3,000 CNY. The majority of the participants (68.03%) were overweight or obese. The average disease course was 10.54 years, and 46.52% of those in the sample had complications. Studies have suggested that marginalized groups generally underutilize health services and that both general demographic characteristics and self-reported health status are important factors when it comes to influencing patients' health need preferences and health service utilization (28). This in turn indicates the importance of exploring influential factors on ITP behavior from the perspective of personal characteristics in order to facilitate the development of more targeted and practical ITP services.

4.1. Overview of patients' behaviors associated with ITP services

Patients' overall behavioral performance associated with ITP services was at a moderately good level (60.78 ± 10.92). The most frequent behaviors were, in order: medication compliance, dietary

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TABLE 1 Basic characteristics of participants.

Variables	Overall	"Low"[†]	"High"	t/χ^2	*P*-value
Sociodemographic data					
Age, years (mean ± SD*)	72.09 ± 5.96	71.65 ± 6.02	72.84 ± 5.80	1.723	0.086
Gender, *N* (%)				0.185	0.693
Male	82 (25.95)	53 (26.77)	29 (24.58)		
Female	234 (74.05)	145 (73.23)	89 (75.42)		
Education level, *N* (%)				2.602	0.635
University and above	5(1.58)	3 (1.52)	2 (1.69)		
Senior high school/technical secondary school	15 (4.75)	10 (5.05)	5 (4.24)		
Junior high school	58 (18.35)	40 (20.20)	18 (15.25)		
Primary school	105 (33.23)	68 (34.34)	37 (31.36)		
Illiteracy	133(42.09)	77 (38.89)	56 (47.46)		
Marriage, *N* (%)				2.865	0.111
Single[#]	82 (25.95)	45 (22.73)	37 (31.36)		
Non-single	234 (74.05)	153 (77.27)	81 (68.64)		
Work, *N* (%)				2.292	0.149
Employed	19 (6.01)	15 (7.58)	4 (3.39)		
Unemployed	297 (93.99)	183 (92.42)	114 (96.61)		
Monthly income, RMB, *N* (%)				3.757	0.345
<3,000	304 (96.20)	191 (96.46)	113 (95.76)		
3,000–5,000	6 (1.90)	2 (1.01)	4 (3.39)		
5,000–8,000	5 (1.58)	4 (2.02)	1 (0.85)		
≥10,000	1 (0.32)	1 (1.01)	0 (0.00)		
Health insurance, *N* (%)				95.198	<0.001
State medicine	1 (0.32)	0 (0.00)	1 (0.85)		
Urban employee basic medical insurance	6 (1.90)	4 (2.02)	2 (1.70)		
Urban-Rural Resident Basic Medical Insurance	259 (81.96)	191 (96.46)	68 (57.63)		
Commercial insurance	1 (0.32)	1 (0.32)	0 (0.00)		
Other[♃]	2 (0.63)	0 (0.00)	2 (1.70)		
None[♄]	47 (14.87)	2 (0.63)	45 (38.14)		
Clinical data					
Disease course[♐], years, (mean ± SD)	10.54 ± 7.32	9.77 ± 6.84	11.85 ± 7.95	2.366	0.019
Body mass index [Ψ], kg/m^2, *N* (%)				2.180	0.688
<18.5	1 (0.32)	1 (0.32)	0 (0.00)		
18.5–24.0	100 (31.65)	64 (32.32)	36 (30.51)		
24.0–28.0	151 (47.78)	90 (45.45)	61 (51.69)		
≥28.0	64 (20.25)	43 (21.72)	21 (17.80)		
Family history[♊], *N* (%)					
Yes	101 (31.96)	67 (33.84)	34 (28.81)	0.858	0.384
No	215 (68.04)	131 (66.17)	84 (71.19)		
Hospitalization history[♋], *N* (%)					
Yes	198 (62.66)	123 (62.12)	75 (63.56)	0.065	0.811
No	118 (37.34)	75 (37.88)	43 (36.44)		

(Continued)

TABLE 1 (Continued)

Variables	Overall	"Low"[Ŧ]	"High"	t/χ^2	*P*-value
Complication of diabetes[ξ], *N* (%)					
Yes	147 (46.52)	92 (46.46)	55 (46.61)	0.001	1.000
NO	169 (53.48)	106 (53.54)	63 (53.39)		
Treatment strategies[§], *N* (%)					
Diet and exercise	1 (0.32)	1 (0.51)	0 (0.00)	7.611	0.046
Oral hypoglycemic agents	155 (49.05)	108 (54.55)	47 (39.83)		
Insulin monotherapy	122 (38.61)	68 (34.34)	54 (45.76)		
Insulin combined with oral hypoglycemic agents	38 (12.03)	21 (10.61)	17 (14.41)		

"Low"Ŧ: the name of cluster 1. Cluster 2 was called as "High".
SD*: standard deviation.
Single#: including divorced or widowed.
Other: other types of insurance except state medicine, urban employee basic medical insurance (UEBMI), urban-rural resident basic medical insurance (URRBMI) and commercial insurance.
Noneħ: without any health insurance.
Disease course (DC): Interval between diagnosis of diabetes and completion of questionnaire.
Body mass indexΨ (BMI): according to National guidelines for the prevention and control of diabetes in primary care (2018), BMI (18.5–24.0) is normal, BMI (24.0–28.0) meaning overweight and BMI (≥28.0) indicates obesity.
Family history¤ (FH): Whether a blood relative had diabetes.
Hospitalization history (HH): Whether the participant had experienced hospitalization due to diabetes.
Complication of diabetesξ (CD): various complications of diabetes including hypertension, and other chronic diseases.
Treatment strategies§ (TS): were divided into non-pharmacological diet and exercise, oral hypoglycemic agents (OHAs), mono-insulin therapy, and insulin combined with oral hypoglycemic agents (combination therapy).

control, and exercise, according to the score rates of each behavioral dimension. This is in line with previous studies reporting that maintaining a healthy diet and high adherence to drug use are the most common behaviors among T2DM patients (29, 30). The result may be explained by the fact that relatively simple care strategies, such as diet control and medication compliance, are easier to put into practice than other measures of T2DM health management (31). Grant also reported high self-reported medication compliance among diabetic patients, positing that inefficient medications, adverse side effects, or patients' lack of belief in the ability of medications to control their illness were the main causes of low compliance in the past (32). The low-frequency behaviors were ranked in order: complications screening, public health service utilization, and foot care. Patients typically neglect daily foot care because only 5.6% of patients have diabetic feet, and some patients think that asymptomatic feet don't need to be checked frequently (33). Less than 15% of patients were checked for diabetic retinopathy and renal disease in the past year, according to the Davis Kibirige research (34), which unquestionably validates our findings about the low frequency of complication screening. Other than foot care, complication screening and public health service utilization are activities that cannot be done alone and often rely on physicians or health care institutions for their implementation. Trust and collaboration issues in the healthcare environment may affect patients' frequent or deep contact with healthcare providers (35).

The classification of patients' behaviors associated with ITP services based on data was reproducible, and the distribution made sense and was generally compatible with the state of health self-management (36, 37). Based on the behaviors scores, the patients in this study were clustered into "Low" and "High" groups. The two groups had a propensity to polarize on each behavioral dimension, as shown in Table 2. The "High" group performed superior to the "Low" group on all behavioral dimensions. This is similar to Nobel's findings, reinforcing the idea that people prefer to focus on the extremes of the range when making health-related decisions (38). The formulation of efficient and holistic preventive health interventions can be influenced by knowledge of whether and which risk factors are clustered together (39, 40). Accordingly, we believe that it is crucial to investigate socio-demographic information related to behavioral variations between the two groups is of great significance for the targeted development of health promotion strategies.

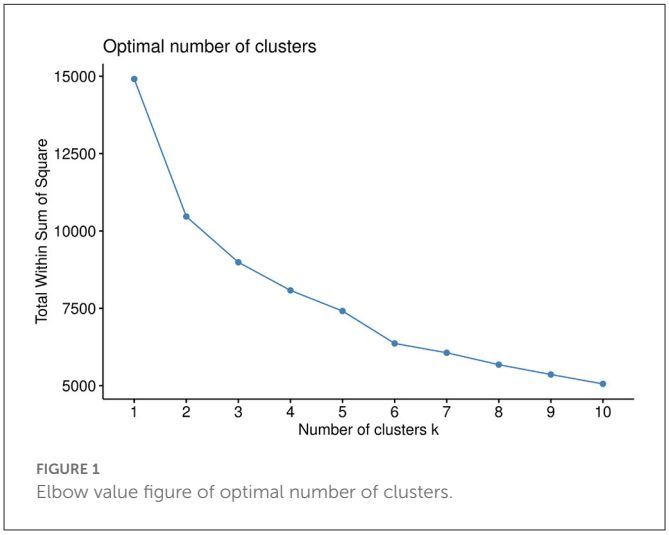

FIGURE 1
Elbow value figure of optimal number of clusters.

4.2. Complication screening

Comorbidity examination is the behavior that T2DM patients tend to overlook the most. The distribution statistics of "excellent, moderately good, and poor" in each behavioral dimension were conducted in two groups in accordance with the score index (Table 3),

and it was discovered that the proportions of "poor performers" in the "Low" group (66.16%), and "moderately good performers" in the "High" group (66.95%) were the highest among both groups respectively. A combination of different elements ostensibly caused this disparity. There is proof that demographic traits and clinical indicators are positively correlated with patients' compliance with complication examination (41). Advanced age, higher socioeconomic level, better education, longer disease duration, more severe disease conditions, or well-controlled blood sugar often prompt patients to participate more actively in complication examination (42–44). The "High" group has a longer disease course which, consistent with the existing evidence, could explain the greater willingness of these patients to engage with complication examination. The treatment strategy is a further factor affecting patients' behaviors. According to the regression analysis, combination therapy had a beneficial effect on patients' behaviors since its behavior scores were 5.980 higher than those of the non-pharmacological treatment group. As stated in the literature, the advancement of T2DM symptoms frequently requires the prescription of insulin (45). On this basis, we speculated that the "High" group's increased use of insulin may be related to their inability to control their blood sugar. Uncontrolled blood sugar will motivate patients to take an active role in their health and disease prevention, but its specific mechanism of action needs to be further studied. Yi-Lin Hsieh explored the factors influencing patients' intention to receive complication examinations. They discovered that the participants' perceptions of barriers to receiving diabetes complication examinations and perceived susceptibility to such issues affected their intentions to get foot and renal screenings (46).

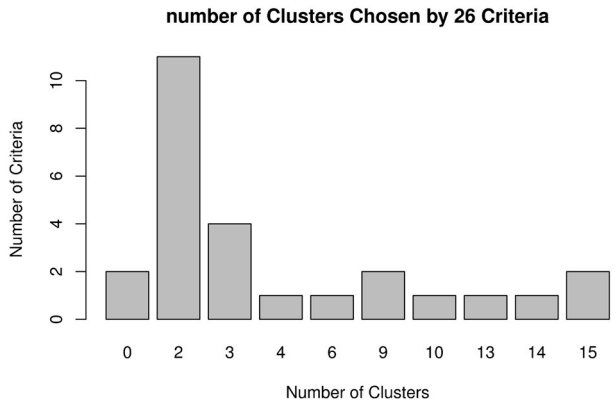

FIGURE 2
Number of clusters chosen by 26 criteria.

4.3. Public health service utilization and foot care

The "High" group performed significantly better than the "Low" group in terms of public health service utilization and foot care, with an average of 4.92 and 4.34 points higher, respectively. A shorter duration of diabetes in the "Low" cluster of patients in this study may be one of the reasons why fewer patients visited health centers, as health status was found to be a determinant of community health services utilization (47). It has been documented that people who report better health are less likely to use healthcare services (48). Besides, most of these patients in the "Low" cluster had better family and social support, were more likely to be married or cohabiting and in employment, and had higher instances of health insurance, which encouraged patients to have more confidence and motivation to adopt healthy maintenance behaviors and often meant that these patients were more likely to have adequate resources and support when coping with adverse events (49, 50). Research has proven that the employed and patients with health insurance

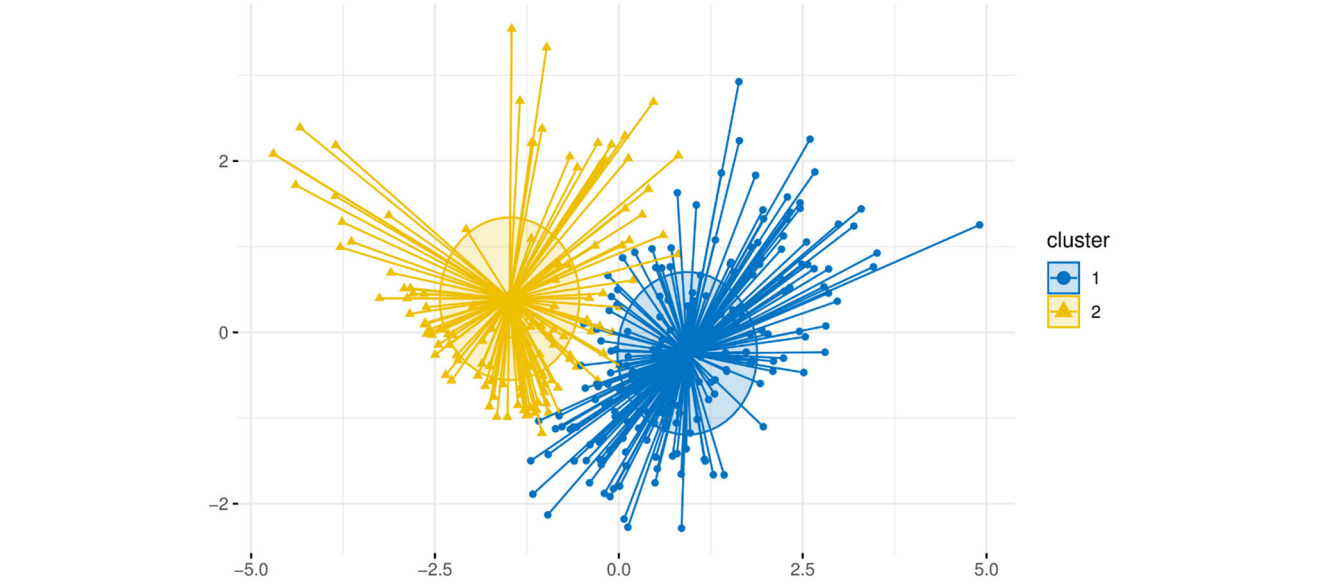

FIGURE 3
K-means clustering result. Cluster 1 (n = 198) named "Low", presented lower scores in the behavior subscale. Cluster 2 (n = 118), assigned as "High", scored higher on all dimensions of behaviors associated with ITP services.

TABLE 2 Total and dimension scores of behavior subscale.

Variables	Score	Score rate$^{\Gamma}$ (%)	Rank	"Low"	"High"	*t*	*P*-value
Total score	60.78 ± 10.92	63.98	–	54.41 ± 6.32	71.46 ± 8.35	19.149	<0.001
Dietary therapy	13.39 ± 2.17	89.27	2	12.97 ± 2.27	14.10 ± 1.78	4.928	<0.001
Exercise	7.58 ± 2.18	75.80	3	6.97 ± 2.07	8.61 ± 1.95	6.973	<0.001
Foot care	9.41 ± 3.01	62.73	5	7.79 ± 1.82	12.13 ± 2.63	15.813	<0.001
Prescribed medication	4.65 ± 0.58	93.00	1	4.53 ± 0.66	4.85 ± 0.35	5.666	<0.001
Glucose and blood pressure monitoring	9.65 ± 2.40	64.33	4	9.15 ± 2.23	10.50 ± 2.44	5.040	<0.001
Complication examination	6.06 ± 3.12	40.40	7	4.81 ± 1.98	8.14 ± 3.56	9.337	<0.001
Access to public health services	10.03 ± 3.60	50.15	6	8.20 ± 2.47	13.12 ± 3.06	14.835	<0.001

Score rate$^{\Gamma}$ = (average score/the highest possible score) × 100.

TABLE 3 Distribution characteristics of ITP behavior in two clusters.

Variables	Item$^{\zeta}$	"Low"			"High"		
		Excellent$^{\tau}$	Moderate$^{\xi}$	Poor$^{\phi}$	Excellent	Moderate	Poor
Total score	19	0 (0.00)	197 (99.49)	1 (0.50)	30 (25.42)	88 (74.58)	0 (0.00)
Dietary therapy	3	162 (81.82)	36 (18.18)	0 (0.00)	109 (92.37)	9 (7.63)	0 (0.00)
Exercise	2	84 (42.42)	104 (52.53)	10 (5.05)	88 (74.58)	27 (22.88)	3 (2.54)
Foot care	3	5 (2.53)	183 (92.42)	10 (5.05)	71 (60.17)	47 (39.83)	0 (0.00)
Prescribed medication	1	191 (96.46)	6 (3.03)	1 (0.50)	118 (100.00)	0 (0.00)	0 (0.00)
Glucose and blood pressure monitoring	3	24 (12.12)	160 (80.81)	14 (7.07)	34 (28.81)	80 (67.80)	4 (3.39)
Complication examination	3	2 (1.01)	65 (32.83)	131 (66.16)	22 (18.64)	79 (66.95)	17 (14.41)
Access to public health services	4	0 (0.00)	121 (61.11)	77 (38.89)	30 (25.42)	88(74.58)	0 (0.00)

Item$^{\zeta}$: the number of entries for behavior subscale and each dimension.
Excellent$^{\tau}$: good performance of integrated treatment and prevention (ITP) behavior (score index ≥ 80%).
Moderate$^{\xi}$: the ITP behavior of diabetics was moderately good (40%≥ score index<80%).
Poor$^{\phi}$: the performance of ITP behavior in diabetic patients was poor (score index <40%).

TABLE 4 A correlation matrix of variables.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Age	1													
Gender	−0.074	1												
Education	0.161**	0.403**	1											
Marriage	0.172**	0.103	0.092	1										
Work	0.295**	0.093	0.218**	0.028	1									
Income	−0.333**	−0.197**	−0.274**	0.036	−0.252**	1								
Insurance	0.085	0.058	0.167**	0.152**	0.125*	−0.102	1							
DC	0.114*	0.092	0.136*	0.060	−0.023	−0.100	0.070	1						
BMI	0.141*	−0.058	0.027	0.090	0.042	−0.020	0.061	0.024	1					
FH	0.138*	−0.112*	0.039	−0.059	0.141*	−0.087	0.081	−0.117*	−0.001	1				
HH	0.040	0.024	0.039	−0.009	0.113*	−0.045	0.104	−0.046	0.085	0.080	1			
CD	−0.108	−0.074	−0.053	−0.128*	−0.129*	−0.012	0.140*	−0.073	−0.065	0.041	0.169**	1		
TS	−0.012	0.043	0.039	0.072	−0.041	0.083	0.021	0.324**	0.009	−0.020	−0.260**	−0.140*	1	
TSB$^{\$}$	0.057	0.018	0.023	0.105	0.100	−0.029	0.493**	0.134*	−0.013	0.051	0.074	0.007	0.194**	1

$^{**}p < 0.01$; $^{*}p < 0.05$.
TSB$^{\$}$: total score of behavior (TSB), sum of scores for each dimension of the behavioral subscale.

TABLE 5 The association between sociodemographic variables, clinical data, and ITP behaviors.

Variables	B	95% CI of B	Beta	*t*	*p*-value	VIF
Constant	72.765	(70.200, 75.331)		55.798	0.000	
UEBMI	−18.095	(−25.923, −10.268)	−0.227	−4.548	0.000	1.097
URRBMI	−15.085	(−17.863, −12.307)	−0.532	−10.684	0.000	1.096
Combination therapy	5.980	(2.843, 9.117)	0.178	3.751	0.000	1.000

tend to seek higher quality health services and technology at high-level hospitals and have less trust in community health centers (51, 52), which also gives some support to our regression results "compared with the uninsured, the UEBMI and URRBMI groups had 18.095 and 15.085 lower behavior scores, respectively." Based on the above factors, we considered that better self-condition and adequate psychosocial coping resources increased to some extent the possibility of cross-level medical treatment and health care in the "Low" cluster of patients, which results in low utilization of primary health services (PHS). The low score for diabetic foot care in this study is consistent with previous research (53). Studies have shown that foot care is related to the duration of diabetes, medication, knowledge of diabetes and attitudes toward diabetes. The higher the education and awareness of diabetes, the better the foot care behavior (54). However, it was also reported that participants' knowledge of diabetes did not translate into action to prevent foot problems, suggesting that we need to consider specific individual characteristics and individual interactions with the environment when designing educational interventions (55).

D'Souza et al. indicated that the main predictors of self-care behavior were demographic and clinical characteristics (56). However, we found that only 29.4% of the variance in individuals' behaviors associated with ITP services was explained by demographic and clinical characteristics. We did not believe that demographic characteristics provided valid starting point for the purposes of considering patients' behaviors associated with ITP services for the treatment of T2DM in this instance. Most current interventions for chronic disease have focused on highly variable factors, such as attitudes or beliefs about illness or health. The literature suggests that patients' attitudes or beliefs about disease or health to a large extent affect the practice of receiving an examination of diabetes complications (46). A large amount of evidence has proved the effectiveness of health belief model (HBM) in predicting health behaviors (57, 58). This suggested that by bolstering health education and promoting diabetes management services, it was possible to increase patients' knowledge and self-efficiency while also increasing their intention to use ITP services. The literature states that chronic care is best delivered in collaboration, however, the fragmentation of healthcare systems may preclude this collaboration, and patients with chronic diseases frequently experience obstacles due to a lack of coordination and continuity in the healthcare system (35). As described in the Institute of Medicine Crossing the Quality Chasm report, contemporary healthcare delivery is characterized by frequent handoffs between providers, insufficient clinical follow-up, and a lack of time and resources to train patients in self-management. As a result, establishing the "partner stickiness" between patients and providers, as well as enhancing providers' patient-centered attitudes and behaviors, can be regarded as one of the effective ways to help patients improve their trust in the healthcare system and their self-care ability (35, 59). Additional goals include strengthening and broadening the primary healthcare system's health reform, enhancing the quality of primary health services, ensuring that patients receive individualized, high-quality care, defending the rights of marginalized groups, and eradicating health disparities.

5. Implications

This study has value both from a theoretical perspective and in terms of practical application: Firstly, it can provide a reference for the exploration and practice of a new model of ITP services for T2DM. This study identified T2DM patients' typical behaviors associated with ITP services in the community, and conduct a preliminary study of its influencing factors, which can serve as a useful guide for how to provide better community ITP services for patients. Secondly, this study makes unique contribution to the optimization of community health management strategies for T2DM, which may be used by community health institutions and CDCs to evaluate the implementation effect of ITP services and to develop personalized intervention measures for patients. Targeted optimization strategies should be adopted for the factors that lead to the formalistic and ineffective ITP services for T2DM in the community. These strategies will be crucial in promoting the modification and optimization of the structure and layout of medical resources, further improving the division of labor and cooperation mechanism of medical alliances, and improving the efficiency of diabetes prevention and control.

6. Limitation

The limitations of our study are briefly described below. Firstly, the patients' behaviors were roughly clustered into two categories in this study and more detailed profiles of behaviors may require more data support to achieve. Secondly, the behavioral data collected in this study are all self-reported by patients. As such, the results may be affected by social desirability bias and recall bias, and the behavior associated with ITP services may be overestimated to a certain extent. Thirdly, the study participants were recruited from a community health center in Nanjing, which may affect the representativeness of the general population. For this reason, future research should include diverse populations. Finally, the convenience sampling will cause some systematic errors, which cannot promote external validity, resulting in the findings lack of generalizability. While this method is suitable for exploratory research, future studies will try to introduce randomization to reduce the allocation and selection bias. The results of this study should be interpreted in an explorative manner

due to the small sample size. In the future, a large sample size should be pursued, which should be sufficient to eliminate type I and type II statistical errors, improving the reliability of research.

7. Conclusion

Studies have shown that the basic demographic characteristics of patients can only explain 29.4% of the variation in patients' behavior associated with ITP services. Therefore, we believe that by strengthening the primary healthcare system, rationalizing the allocation of health resources, and improving the professional training of medical personnel starting from the policy and environment, and concentrating on the utilization of complication screening, foot care, and public health services as a breakthrough we can improve the willingness of T2DM patients to engage in ITP services. This would, in turn, result in the provision of better ITP services for T2DM patients with different backgrounds, enhance the health management of T2DM patients, and achieve better overall health outcomes.

Data availability statement

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

Author contributions

The data was collected by RZ, NZ, SW, XZ, LP, BD, YL, and WM. The field survey was coordinated with the help of BD, YL, and WM. Statistical analysis was performed by RZ and NZ. The manuscript was written by RZ. The study was conceived and manuscript was reviewed and edited by HF. All authors approved the final version of the manuscript.

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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.2022.1084946/full#supplementary-material

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Idealistic, realistic, and unrealistic expectations of pharmacological treatment in persons with type 2 diabetes in primary care

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Introduction: Information on treatment expectations in diabetes is scarce for Mexican and Latino populations. We determined idealistic, realistic, and unrealistic expectations for metformin, insulin, and glyburide in primary care. We also explored the association between sociodemographic attributes, time since diagnosis, and expectations.

Methods: This was a cross-sectional study conducted during 2020–2022 in governmental primary care centers. We consecutively included persons with type 2 diabetes aged 30–70 years under pharmacological medication ($n = 907$). Questions were developed using information relevant to expectation constructs. Data were collected by interview. We used descriptive statistics, a test of the difference between two proportions, and multivariate ordinal logistic regression.

Results: A high percentage of participants would like to have fewer daily pills/injections or the option of temporarily stopping their medication. Realistic expectations ranged from 47% to 70%, and unrealistic expectations from 31 to 65%. More insulin users wished they could take a temporary break ($p < 0.05$) or would like to be able to change the route of administration ($p < 0.001$) than metformin users. More persons with diabetes on insulin expected realistic expectations compared to those on metformin or glyburide ($p \leq 0.01$). Being able to interrupt medication upon reaching the glucose goal was higher in combined therapy users ($p < 0.001$).

Conclusion: Time since diagnosis, place of residence, sex, and diabetes education were factors associated to expectations. Management of expectations must be reinforced in primary care persons with type 2 diabetes undergoing pharmacological medication.

KEYWORDS

expectations, diabetes, primary care, therapeutic misconception, individual preference

1. Introduction

Diabetes is a chronic condition characterized by high blood glucose levels, which, if left untreated, leads to heart, vascular, eye, kidney, and nerve complications. There are two main types of diabetes: type 2 and type 1. The first is initially due to insulin resistance that progresses to loss of adequate insulin secretion by b-cells. Type 1 is an insulin-dependent diabetes, in which the pancreas produces little or no insulin by itself due to autoimmune b-cell destruction (1, 2). Type 2 diabetes is the most common type accounting for over 90% of all diabetes cases worldwide. An estimated 537 million adults aged 20–79 years were living with diabetes

in 2021 (10.5% prevalence); 50.5 million in the North America and Caribbean region (14.0% prevalence) and 32.5 million in the South and Central America region (9.5% prevalence). Mexico is among the top 10 countries for diabetes, with 14.1 million people affected (15% prevalence) (2). Regular physical activity, a healthy diet, and a healthy body weight are key factors that must be promoted by public and private health institutions since they are the foundation of type 2 diabetes management. If the adoption of healthy habits does not achieve optimal glucose levels, pharmacotherapy should be initiated. Metformin is one of the first-choice oral medications. If a single diabetes-specific medication does not work, a range of combination therapy options are available (sulfonylureas, thiazolidinediones, and alpha glucosidase inhibitors, among others). Additionally, insulin injections may be needed to reach glycemic goals (3, 4). From 25 to 90% of persons with type 2 diabetes do not take medication as prescribed (5). Differences in managing diabetes expectations between the diabetes care team and persons living with diabetes lead to inconsistencies in taking medication because those who notice no benfit may stop taking them (6). Meeting expectations is important because the individual may think medication does not work (7), and dissatisfied persons are less likely to follow the medication plan or to take an active role in their care (8). The loss of continuity in taking the medication will, in turn, decrease therapeutic efficacy, with consequences on target glucose levels (9–11), hospitalization (5, 10), mortality (5, 12), and high costs (10, 13). Therefore, awareness of personal expectations is essential for healthcare professionals, health managers, and health policymakers.

An expectation refers to the anticipation of the occurrence of a specific outcome. It is a type of belief or perception of a future event. The theory of expectations in psychology maintains that they are the product of a cognitive process dependent on experience and social learning (14, 15). The individual compares what is anticipated with what is received and confirms or modifies his/her expectations. He/she also compares results with other individuals, medications, and health conditions (7, 16). There are structural (e.g., tablet shape and color) and process (e.g., medication procedure) expectations. For instance, an injectable medication may be anticipated to be more effective than an oral one, or a medicine prescribed by a cardiologist may be anticipated to be more effective than one prescribed by a general practitioner (15). Expectations can be idealistic (what the person wants or prefers if given the choice), unrealistic (myth or fantasy), or realistic (predictive). Moreover, realistic expectations can be positive (e.g., symptom relief, hospitalization prevention, goal achievement) or negative (e.g., adverse effect experience) (7, 14, 15, 17). The literature on realistic expectations show 70% of persons living with diabetes on oral medication anticipate the benefit of achieving target glucose levels and only 11.7% expect a reduction in the risk of complications (18). One study found that only one-fifth of persons with diabetes expected to take glucose-lowering agents for the rest of their lives (19). Moennig et al. (20) found that 42% of insulin users expected an improvement in glucose, and fulfillment of this expectation was the main cause of uninterrupted use. Naegeli et al. (21) documented a higher percentage of insulin users anticipate achieving optimal glucose levels (61%). Notably, 58% had their expectations exceeded and 29% their expectations fulfilled. On the other hand, the following erroneous expectations have been reported: being able to stop the medication when reaching the glucose goal, anticipating diabetes cure, and expecting freedom to eat while taking the medicine (18, 19, 22–26). The study of expectations in diabetes is worthwhile because persons living with diabetes with positive outcome expectations are more likely to benefit from diabetes management than those with negative outcome expectations (27), while idealistic expectations or misperceptions seem to have the opposite effect on health outcomes (15).

Personal expectations may vary according to ethnic origin, age, sex, socioeconomic status, schooling, diabetes education, time since diagnosis, and diabetes severity (14, 22, 28). However, information on expectations and associated factors in persons with diabetes is practically non-existent in Mexican or Latino populations (24). The objective of this study was to determine the idealistic, realistic, and unrealistic expectations of pharmacological medication (metformin, insulin, and glyburide) among persons with type 2 diabetes in primary care. We also explored the association between sociodemographic attributes (sex, schooling, place of residence, education in diabetes), time since diagnosis, and expectations.

2. Materials and methods

This was a cross-sectional study conducted from October 2020 to March 2022. We consecutively included persons with type 2 diabetes between 30 and 70 years old under pharmacological therapy. Those with current pregnancy or history of blindness, hemodialysis, peritoneal dialysis, lower-extremity amputation, and heart surgery were excluded (to limit persons with advanced diabetes severity among whom expectations might differ from those of persons with mild or no complications). The participants were approached in waiting rooms of primary care centers of a governmental health institution in the metropolitan area of Monterrey (the third-largest urban area of the country, with a population density of 3,523 inhabitants/km^2) and one primary care center in a suburban area located in Linares (population density of 33.7 inhabitants/km^2), Mexico. The prevalence of idealistic, realistic, and unrealistic expectations was taken as the parameter (p) for estimating the sample size. A minimum sample size of 385 individuals with diabetes was required considering $p = 50\%$ with a 95% confidence level and a precision of 5%. However, the total sample size was 907; 507 participants from the urban area and 400 participants from the suburban area. The protocol was approved by the Local Committees of Ethics and Health Research (No. 2020-1909-062, 2021-1909-101, and 20-FASPYN-SA-22.TP). Informed consent was provided by all the participants. Anonymity was always preserved, and the confidentiality of the data was ensured.

2.1. Study variables

Three types of expectations were studied: idealistic, realistic, and unrealistic; and the anticipation of a future event was the common definition. Idealistic expectations focused on management preferences, realistic expectations on perceived medication efficacy, and unrealistic expectations on incorrectly perceived therapeutic benefits. Expectation items were subject to content validity evaluation. A group of experts (three medical doctors and two public health specialists) assessed and approved by consensus the pertinence and relevance of the questions. Special attention was paid to avoiding ambiguity and technical vocabulary. Pre-test and pilot tests were

carried out to verify clarity and ease of understanding. The internal consistency results are provided below.

2.1.1. Idealistic expectations domain

Measurement was based on what the person with diabetes preferred if given the choice. Questions were developed using information relevant to idealistic expectation constructs (14, 15). Three items were included: (1) If you had the option, you would like to take fewer pills or receive fewer applications of insulin per day (in those who took more than one tablet or received more than one application per day); (2) You would like to be able to change the route of administration from oral to injectable, or vice versa; and (3) You wish you could take a temporary break from the medication. In persons treated with metformin, a fourth item on preference for a smaller tablet size was also included. The response options were on a Likert scale (−1 = No, 0 = Indifferent, 1 = Yes). The questions were specific to the medication being received, so an individual on metformin answered the questions about metformin. If someone was on two medications, for example, metformin and insulin, he/she answered the metformin and insulin questions separately (metformin: $n = 725$, Cronbach's Alpha = 0.97; insulin: $n = 352$, Cronbach's Alpha = 0.94; glyburide: $n = 180$, Cronbach's Alpha = 0.68). For the analysis of association, an index was constructed to summarize the idealistic expectations domain. The negative and indifferent responses were regrouped and coded as 0; the positive response remained as 1. Responses were then summed and categorized into null, low, and moderate-high depending on the number of idealistic expectations 0, 1, and 2–3, respectively.

2.1.2. Realistic expectations domain

Measurement was based on the perception of true medication benefits. Six items adapted from other authors (7, 18) were used: (1) How much do you expect the medicine will bring blood sugar down to a normal range; (2) Eliminate symptoms of hyperglycemia; (3) Prevent or delay foot amputations; (4) Prevent or delay the need for dialysis; (5) Prevent or delay vision loss; and (6) Reduce the need for hospitalization. The response options were on a Likert scale (1= Null, 4= Very much). Cronbach's Alpha was as follows: Metformin = 0.92, insulin = 0.90, and glyburide: = 0.90. For the analysis of association, an index was constructed to summarize the realistic expectations domain. The "null", "a little", and "moderately" responses were regrouped and coded as 0; the "very much" response was recoded as 1. Responses were then summed and categorized into null, low, moderate, and high depending on the number of realistic expectations 0, 1–2, 3–4, and 5–6, respectively.

2.1.3. Unrealistic expectations domain

Measurement was based on misperception of medication benefits. Four items adapted from other authors (22–25) were used: (1) How much do you expect the medicine will cure your diabetes; (2) Allow you to stop treatment when reaching your glucose goal; (3) Allow freedom to eat; and (4) Allow you to have no complications despite medication. The response options were on a Likert scale (1=Null, 4= Very much). The questions were generic; for example, a person treated with metformin and insulin answered the section without distinguishing between medications ($n = 907$, Cronbach's Alpha = 0.66). For the analysis of association, an index was constructed to summarize the unrealistic expectations domain. The "a little", "moderately", and "very much" responses were regrouped and coded as 1; the "null" response was recoded as 0. Responses were then summed and categorized into null, low, and moderate-high depending on the number of unrealistic expectations 0, 1, and 2–4, respectively.

2.1.4. Other variables

Sociodemographic attributes (sex, age, marital status, schooling, occupation, place of residence), diabetes education in the last year (yes, no), time since diagnosis (years), and frequency of medical visits for diabetes management (monthly, every 2 months, other) were included. Comorbidities (hypertension, dyslipidemia, other) (yes, no), hospitalization due to diabetes in the past year (yes, no); and last glucose result (mg/dL) (self-report) were also considered. Data were collected through a face-to-face interview lasting approximately 15 min. Two postgraduate students (Family Medicine and Master of Sciences in Public Health) and two medical interns participated. All were supervised by the principal investigator. Participants with incorrect expectations were given the correct information at the end of the survey. Those with idealistic expectations were instructed to express their preferences to their doctor at the next visit, so that they could jointly analyze the possibility of satisfying them.

2.1.5. Statistical analysis

Means and standard deviations were used to describe continuous variables, and percentages to describe categorical variables. The z test for the difference between two proportions was used for comparing the frequency of expectations by type of medication. The chi-square test (univariate analysis) and ordinal logistic regression (multivariate analysis) were employed for analyzing the association between factors under study and expectations; the sociodemographic attributes and time since diagnosis were considered the independent variables; the idealistic, realistic, or unrealistic expectations index constituted the dependent variable; and the comorbidity and frequency of medical visits for diabetes management were the control variables. Odds ratios (OR) and 95% confidence intervals (CI) were estimated for quantifying the strength of the association between associated factors and expectations.

3. Results

The mean age was 55.7 ± 10.6, and the mean time since diabetes diagnosis was 9.9 ± 7.9 years. Most of the participants were female and married or with a partner. More than 80% had routine monthly medical visits for diabetes management. Table 1 shows in detail the sociodemographic and comorbidity profile of the study population.

3.1. Idealistic expectations

A high percentage of participants on metformin would like the pill size to be smaller (77.8%). About 90% would like fewer pills/injections per day. More insulin users wished they could take a temporary break or would like to change the route of

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administration (Figure 1). Suburban residence, ≥ 3 years since diagnosis, and female sex increased the odds of higher metformin idealistic expectations. Place of residence was also associated to glyburide idealistic expectations and time since diagnosis with those of insulin (Table 2).

TABLE 1 Sociodemographic and comorbidity profile ($n = 907$).

Attribute	Frequency
Sex, female	62.3%
Marital status, married or with partner	71.3%
Schooling	
Primary	38.3%
Secondary	29.9%
High school and higher	31.9%
Occupation	
Employed	36.3%
Self-employed	6.3%
Housewife	39.3%
Retired	16.4%
Unemployed	1.7%
History of diabetes education, during last year	20.3%
Diabetes management medical visits, monthly	80.8%
Glucose < 110 mg/dL (self-report)	18.8%
Hypertension	51.0%
Dyslipidemia	42.3%
Other (urinary, circulatory, vision, or neuropathy)	13.0%
History of hospitalization, during last year	1.8%

3.2. Realistic expectations

Between 47 and 70% of participants had realistic expectations; insulin users had more realistic expectations than metformin users (Table 3). Suburban residence and having hypertension and/or dyslipidemia increased the odds of higher metformin realistic expectations (Table 2).

3.3. Unrealistic expectations

The most frequent unrealistic expectation was anticipating complications despite the medication (64.8%). It was followed by expecting interruption of medication upon reaching the glucose goal (55.0%), freedom to eat (39.1%), and diabetes cure (30.7%). Combined therapy users had a higher expectation of being able to discontinue the medication upon reaching the glucose goal (Table 4). Suburban residence increased 1.98 times (95%CI 1.47, 2.68) the odds of higher unrealistic expectations while diabetes education in the last year decreased them (OR 0.62, 95% CI 0.44, 0.87); after adjustment for type of medication, sex, schooling, time since diagnosis, comorbidity, and frequency of medical visits for diabetes management.

4. Discussion

We determined idealistic, realistic, and unrealistic expectations about metformin, insulin, and glyburide in persons with type 2 diabetes in primary care. We found several expectation differences by type of medication. Almost half of the people on insulin would like to be able to switch to oral administration compared to one-fourth on metformin who would like the opposite, indicating that personal preferences should not be taken for granted. Boye et al. (29) evidenced

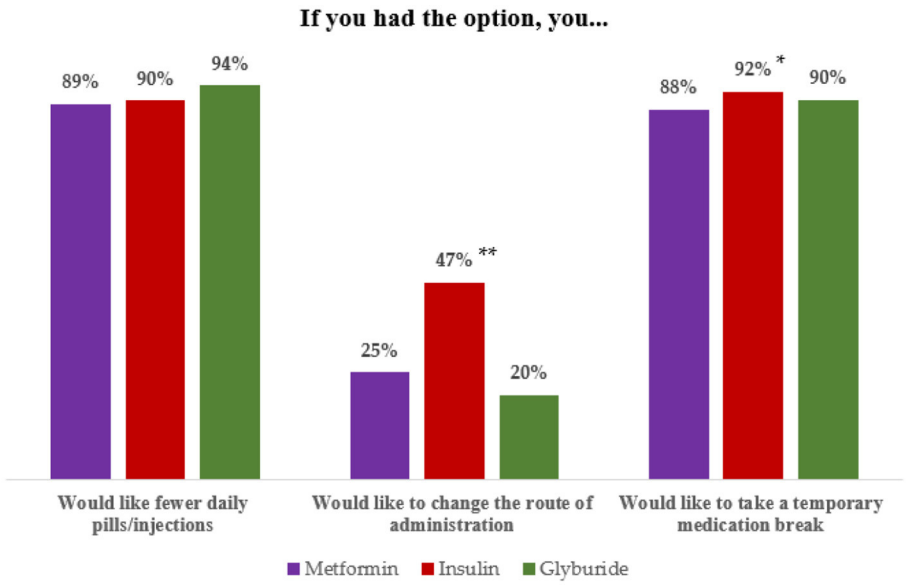

FIGURE 1
Idealistic expectations according to type of medication. Information at the bottom of the figure: z test for the difference between two proportions *p* values: *<0.05, Insulin > Metformin, **<0.001, Insulin > Metformin and glyburide.

TABLE 2 Multivariate ordinal regression analyses of factors associated to idealistic and realistic expectations.

	Type of medication		
	Metformin ($n = 725$)	Insulin ($n = 352$)	Glyburide ($n = 180$)
	Adjusted odds ratios[a] (95%CI)		
Idealistic expectations (moderate-high)[b]			
Residence, suburban	1.6 (1.1, 2.3)**	1.4 (0.7, 2.8)	3.5 (1.7, 7.3)***
Time since diagnosis, ≥ 3 years	2.7 (1.8, 3.9)***	5.5 (2.3, 13.1)***	0.6 (0.2, 1.7)
Sex, female	1.5 (1.1, 2.0)*	0.9 (0.5, 1.7)	1.1 (0.6, 2.2)
Comorbidity, hypertension and/or dyslipidemia	0.8 (0.5, 1.1)	1.3 (0.7, 2.3)	0.9 (0.4, 2.0)
Realistic expectations (high)[c]			
Residence, suburban	1.9 (1.4, 2.6)***	1.6 (0.9, 2.6)	1.4 (0.8, 2.7)
Time since diagnosis, ≥3 years	0.9 (0.6, 1.3)	0.9 (0.4, 1.9)	0.5 (0.2, 1.3)
Sex, female	1.1 (0.8, 1.5)	1.3 (0.8, 1.9)	1.0 (0.6, 1.8)
Comorbidity, hypertension and/or dyslipidemia	1.4 (1.0, 1.8)*	1.3 (0.8, 2.0)	1.2 (0.6, 2.2)

Wald Chi-square p values: * < 0.05, ** < 0.01, *** < 0.001.
[a]Variables present in the model without statistical significance were schooling, diabetes education in the last year, and frequency of medical visits for diabetes management ($p > 0.05$). [b]Index of 2-3 idealistic expectations with an affirmative response (out of a total of 3). [c]Index of 5–6 realistic expectations with a "very much" response (out of a total of 6).

TABLE 3 Realistic expectations according to type of medication.

The medicine will very much…	Type of medication		
	Metformin ($n = 725$) (A)	Insulin ($n = 352$) (B)	Glyburide ($n = 180$) (C)
Bring blood sugar down to a normal range	54%**[a]	70%***[b]	67%
Eliminate hyperglycemia symptoms	47%	59%**[b]	54%
Prevent/delay foot amputation	51%	61%**[b]	54%
Prevent/delay need for dialysis	49%	62%**[b]	50%*[c]
Prevent/delay vision loss	48%	59%*[b]	49%
Reduce need for hospitalization	52%	63%**[b]	57%

z test for the difference between two proportions p values: * ≤ 0.01, ** < 0.001, *** < 0.0001; [a]A < C, [b]B > A, [c]C < B.

25.5% of persons with diabetes had switched from preferring oral to injectable medication after learning about the product specifications (daily oral semaglutide vs. once-weekly injectable dulaglutide). We also identified 8 out of 10 participants on metformin would like the size of the pill to be smaller and a high percentage would like fewer daily pills/injections or a temporary break from the medication. Fairchild et al. (19) documented 78% of adults in primary care did not expect to take oral medications for life. Idealistic expectations must be discussed with the person living with diabetes because the ideal may not be feasible. And personal preferences, shared decision making, and mutual agreement for changes should be encouraged.

There were more real benefits perceived with insulin than metformin. Laferton et al. (15) also showed an injectable medication was expected to be more effective than an oral one. Reduction of glucose to a target level was the number one most expected benefit, 7 out of 10 insulin participants anticipated this result, higher than 42 and 61% reported by multinational studies (20, 21). In contrast, 5 out of 10 metformin users expected this benefit, a result lower than that documented in primary care of 70% (18). Differences in findings emphasize the importance of identifying expectations in different populations. Correspondence between the diabetes care team members and the person with diabetes is essential since it may contribute to non-taking the medication by failing to explain benefits and side effects adequately (30). Realistic expectations must be reinforced, since the greater the perception of effectiveness, the greater the medication taking (31, 32). Furthermore, a low efficacy perception has been associated with higher levels of HbA1c (33).

More than half of the respondents anticipated complications would occur despite treatment or that they could stop the medication when the glucose goal was reached. In Saudi Arabia, these were also the most common unrealistic expectations (89 and 66.5%, respectively) (22). Analysis by type of therapeutic plan showed combined therapy users expected more to discontinue the medication upon reaching the glucose goal. One-third anticipated diabetes would be cured over time with no differences by medication scheme. The frequency of this erroneous expectation has been wide-ranging (11.7–65%) (19, 23–26) and some authors such as Mann et al. (25) have reported insulin users are less likely to

TABLE 4 Unrealistic expectations according to therapeutic plan.

The medicine will very much, moderately, a little...	Therapeutic plan				
	Metformin	Insulin	Glyburide	Metformin + insulin	Metformin + Glyburide
	($n = 375$)	($n = 162$)	($n = 20$)	($n = 190$)	($n = 160$)
	(A)	(B)	(C)	(D)	(E)
Cure diabetes	33.1%	28.4%	20.0%	31.6%	27.7%
Allow stopping treatment when reaching glucose goal	50.9%	47.5%	25.0%	63.2%**[a]	66.3%**[a]
Allow freedom to eat	37.6%	35.8%	45.0%	41.1%	43.1%
Allow complications despite treatment	61.3%	66.7%	50.0%[§c]	64.7%	73.1%*[b]

z test for the difference between two proportions p values: * ≤ 0.01, ** < 0.001, § $= 0.06$; [a]D and E > A, B, and C, [b]E > A, [c]C < E.

believe in diabetes cure. Additionally, over a third of participants expected they could eat anything while taking the medication. Literature reports vary from 23 to 49.1% (23, 24, 26). Food freedom means always eating what you want in the amount you want. Freedom might be an exception, but not the rule. Medical nutrition therapy plays an integral role in diabetes management that considers maintaining the pleasure of eating by providing flexibility with healthy food choices, while limiting unnecessary and unhealthy ones. The American Diabetes Association advises people with diabetes to minimize the consumption of foods with added sugar and refined grains. It also emphasizes the consumption of polyunsaturated fats and limits the serving size of nutrient-dense foods for favoring a healthy body weight and achieving glucose and lipid goals (34). Certainly, knowledge and beliefs about medications should be attended to. Health educators and decision makers should keep in mind that outcome expectations and self-care behaviors are correlated (35, 36), and that unrealistic expectations constitute barriers to effective diabetes management. Clearly, the insertion of effective health communication strategies is urgently needed to neutralize misconceptions, such as the diabetes cure, and to reinforce true facts.

We explored the association between several factors and expectations, ≥3 years since diagnosis increased the odds of higher metformin and insulin idealistic expectations indicating need for matching correct information over time. Time since diagnosis was not associated to unrealistic expectations, which differed from other studies that have shown greater misperceptions with < 5 (26) or between 5 and 15 years with diabetes (22). This lack of consistency requires further research. Being female increased the odds of metformin idealistic expectations, but not those of erroneous expectations. Other authors have identified women tend to have higher misconceptions (22, 26). Suburban residence was another associated factor. It augmented the odds of metformin idealistic and realistic expectations, also the odds of glyburide idealistic expectations, and those of unrealistic expectations. There are three ways to create expectations: direct personal experience, observation, and suggestion of others (27). Dissimilarity in such circumstances could explain differences between urban and non-urban residents, but more investigation is needed to identify the specific reasons. Diabetes education in the last year lessened the odds of misperceptions. Alsunni et al. (22) found individuals who had undergone proper education about diabetes had less misconceptions, underlining the importance of educational programs. Diabetes self-management education is essential in the care of all people with diabetes to provide knowledge and skills. And the 2022 National Standards for Diabetes Self-Management Education and Support recommend the collaboration between the person and the health care team considering the individual's concerns, needs and priorities (37).

4.1. Limitations

Obtaining socially acceptable responses could have led to overestimation or underestimation of expectations. This study focused on the most frequently employed diabetes medication, so dipeptidyl peptidase 4 inhibitors (DPP-4), thiazolidinediones, and sodium glucose co-transporter 2 inhibitors users were not considered. Only persons with diabetes from primary care without current pregnancy or advanced complications were included, so it is not possible to generalize results to those with gestational diabetes or under diabetes management in secondary or tertiary care. More research is needed, and future investigations should include these types of cases. More than half of the study population were women, which was not surprising. In Mexico, there are more women than men according to the 2020 population census and diabetes is more prevalent in women (38, 39). The association analysis had the advantage of being multivariate, but the study design was cross-sectional. Future longitudinal studies are required for definitive conclusions on factors determining idealistic, realistic, and unrealistic expectations.

5. Conclusions

This study contributes to narrowing the knowledge gap about idealistic, realistic, and unrealistic expectations in the Mexican or Latino population regarding pharmacological medication in persons with type 2 diabetes. The frequency varied by expectation and type of medication. Insulin users had more idealistic and realistic expectations; and combined therapy users expected more to discontinue the medication upon reaching the glucose goal. Time since diagnosis, place of residence, and sex were factors associated to expectations. Especially, diabetes education reduced the odds of misperceptions. Health policy makers, health managers, and the diabetes care team together must ensure that people with diabetes be trained. Understanding personal preferences and expectations is relevant because it makes it easier to select the medication that will most benefit the individual. A person-centered

communication, shared decision making, and management of expectations must be reinforced in persons with type 2 diabetes undergoing pharmacological medication in primary care.

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 Institutional Review Board and Ethics Committee of the Mexican Social Security Institute (No. 2020-1909-062 and 2021-1909-101) and the School of Public Health and Nutrition (20-FASPYN-SA-22.TP). The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization and methodology: AS and AJ. Data curation and investigation: AJ, YR, and LH. Formal analysis and validation: AS and HC. Project administration: AS, FG, and GN. Supervision and writing—original draft: AS. Writing—review and editing: AS, AJ, YR, HC, FG, LH, and GN. All authors contributed to the article and approved the submitted version.

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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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Serum cotinine as a predictor of lipid-related indices in Turkish immigrants with type 2 diabetes: A clinic-based cross-sectional study

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Background: Turkish immigrants form the largest ethnic minority group in the Netherlands and show a higher prevalence of (i) cardiovascular disease (CVD), (ii) cigarette smoking, and (iii) type 2 diabetes (T2D) as compared to the native Dutch. This study examines the association of CVD risk factors: serum cotinine, as an indicator of cigarette smoke, and lipid-related indices among first-generation (foreign-born) Turkish immigrants with T2D living in deprived neighbourhoods in the Netherlands.

Methods: A total of 110 participants, physician-diagnosed with T2D, aged 30 years and older, were recruited by convenience sampling from the Schilderswijk neighbourhood of The Hague in a clinic-based cross-sectional design. Serum cotinine (independent variable) was measured with a solid-phase competitive chemiluminescent immunoassay. Serum lipids/lipoproteins (dependent variables) were determined by enzymatic assays and included: total cholesterol (CHOL), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and triglycerides (TG). The Castelli Risk Index-I (CRI-I), and Atherogenic Coefficient (AC) were calculated using standardised formulas and assessed as dependent variables in multiple linear regression (MLR) models. Log-transformation of HDL-c, TG, CRI-I, and AC values were performed to account for the extreme right skewness of the data. Statistical analyses included descriptive characteristics and MLR models were adjusted for all major confounders of cotinine and lipids.

Results: The sample size had a mean age of 52.5 years [standard deviation (SD) = 9.21]. The geometric mean of serum cotinine level was 236.63 ng/mL [confidence interval (CI) = 175.89 ± 318.36]. The MLR models indicated that high serum cotinine levels (≥10 ng/mL) was positively associated with HDL-c (P = 0.04), CRI-I (P = 0.03), and AC (P = 0.03) in the age, gender, WC, diabetes medications, and statins-adjusted models (n = 32).

Conclusion: This study indicated that lipid ratios of HDL-c, CRI-I and AC are dependent determinants of serum cotinine and higher serum cotinine levels (≥10 ng/mL) are associated with worse HDL-c, CRI-I and AC values in participants with T2D. Clinical comprehension of these biochemical indicators (lipids/lipoproteins) and symptomatic results (CVD risk) in individuals with T2D will aid in the intervention (smoking) approach for this vulnerable cohort (Turkish immigrants). Therapy that is targetted to modify this behavioural risk factor may

improve cardiovascular health outcomes and prevent comorbidities in Turkish immigrants with T2D living in deprived neighbourhoods in the Netherlands. In the meantime, this report contributes to a growing body of information and provides essential guidance to researchers and clinicians.

KEYWORDS

cardiovascular disease, cotinine, diabetes, immigrants, lipids, neighbourhood deprivation, smoking

Introduction

Type 2 diabetes (T2D) is highly prevalent among ethnic minorities living in Western societies. Comparable to other Western countries such as the United Kingdom and the United States of America (USA) (1–3) the overall cardiovascular mortality is typically higher among ethnic minority groups as compared to the general population of the Netherlands (4). In the Netherlands, Turkish immigrants form the largest ethnic minority group with 429,978 inhabitants according to 2022 census (5). Epidemiological studies report that people living in deprived neighbourhoods have an increased risk for developing cardiovascular diseases (CVD) as compared to the general population (6). The Hague, Netherlands, a city that is part of the Randstad metropolitan area, is vastly urbanised with a large population of Turkish immigrants (n = 75,423). The Schilderswijk neighbourhood is considered a deprived area of The Hague populated by 91.8% non-Western immigrants and 8.2% native Dutch (7, 8). According to Gemeente Den Haag census, Turkish immigrants are the most prevalent inhabitants of the Schilderswijk area (n = 4,005) (8). Furthermore, 61.3% residents in the Schilderswijk area are aged 20–64 years, with an average age of 35 years (8). Kriegsman et al. (9) indicate that the onset of diabetes occurs one decade earlier among the Turkish when compared to the native Dutch. Moreover, scientific literature identifies mortality from CVD in patients with T2D to be higher than in the general population (10, 11).

Diabetes, cigarette smoking, and dyslipidaemia are well-known risk factors for CVD in the general population in the Netherlands (12). Compared to the native Dutch population, Turkish immigrants in the Netherlands show a higher prevalence of (i) CVD, (ii) cigarette smoking, and (iii) T2D (9, 13–16). However, El Fakiri et al. (17) indicate that ethnic minorities are less likely to smoke as compared to the native Dutch (OR = 0.10–0.53). Yet, data from the Lifestyle in Amsterdam: Study among Ethnic gRoups (LASER)-study (16) report a higher prevalence of smoking in first-generation Turkish males and second-generation Turkish females as compared to native Dutch males and females. Hosper et al. (16) suggest that the smoking prevalence rates of second-generation Turkish males are comparable to the prevalence rates among Dutch males. Recently, Jain and Ducatman (18) analysed data from the National Health and Nutrition Examination Survey (NHANES) for the period 1999–2012 to examine the effect of serum cotinine (<10 ng/ml classified as non-smokers, ≥10 ng/mL classified as smokers) on the levels of total cholesterol (CHOL), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and triglycerides (TG) for the US population aged ≥20 years. Findings of the aforementioned study suggest that serum cotinine is significantly associated with unfavourable lipid/lipoprotein profiles among the adult population of the USA. The clinical use of serum cotinine, rather than self-reported smoking status, in epidemiological studies has added to our understanding of the association between cigarette smoking and adverse lipid profiles. It is important to examine molecular biomarkers of modifiable health risks among high-risk populations and serum cotinine may be a better indicator of quantifying risks from cigarette use as opposed to self-reports (19).

Research indicates that Turkish immigrants in the Netherlands are 2.4 times more likely to be obese, but have a lower prevalence of hypercholesterolaemia (17). According to the 2002 Rijksinstituut voor Volksgezondheid en Milieu (RIVM) report (13), 80% of Turkish immigrants aged 35 years or older are overweight. A cross-sectional study done among Turkish and Moroccan migrants in the Netherlands, show that specific subpopulations are at particular risk for overweight and obesity and ethnic-specific interventions should address all first-generation immigrants (20). Little is known about the association of serum cotinine and lipid abnormalities among first-generation Turkish immigrants with T2D. Considering the high prevalence of smokers among the Turkish population in the Netherlands (16), it is more than likely that a significant amount of the population who do not smoke may be exposed to second hand smoke exposure (SHS). Additionally, the increased prevalence of smoking among first-generation Turkish immigrants may be related to external stressors such as being diagnosed with T2D and/or living in deprived neighbourhoods. Therefore, the objective of this study was to examine the relationship between serum cotinine, as an indicator of cigarette smoke, with lipid-related indices among first-generation Turkish immigrants with T2D living in deprived neighbourhoods of The Hague, Netherlands.

Materials and methods

Participants

The study population consist of 110 first-generation Turkish immigrants, physician-diagnosed with T2D, aged 30 years and older. First-generation Turkish immigrants were defined according to the definition of Statistics Netherlands for non-Dutch first-generation: born outside the Netherlands with one or both parents born outside the Netherlands (21, 22). All participants were diagnosed with T2D as recommended by the 2006 Nederlands Huisartsen Genootschap (NHG) standard and/or use of diabetes medication (23).

Sampling

The investigation took place from March to May 2011 in a clinic-based cross-sectional design. Turkish immigrants were recruited from the deprived Schilderswijk area of The Hague. Neighbourhood deprivation in the Netherlands was determined according to a validated index (7). **Supplementary Figure 1** illustrates the convenience sampling design used for participant recruitment in this non-randomised cross-sectional study. During the 3-month period, 300 letters written in Dutch and Turkish languages outlining the study were mailed to residents of the Schilderswijk area with Turkish surnames listed in the local telephone directory. The interested participants could respond to the invitation letter. Due to unknown addresses, 1% of the unopened letters were returned undeliverable. Posters and flyers were also displayed at general practitioner (GP) offices, dieticians' offices, health club centres, mosques, hair salons, Turkish grocery stores, community centres, and pharmacies where Turkish immigrants were known to frequently visit. Local GP's actively told their patients about, and referred them to, our research study. From this, 11 eligible participants were enrolled from the delivered mail, 60 participants were enrolled from GP offices, and 20 participants from posters and flyers. Recruitment of participants through word of mouth was actively promoted by a Turkish community representative in the Schilderswijk area, where participants of the study were encouraged to recruit other participants (n = 19 eligible participants). Twenty-two potential participants did not qualify for the study because they were either not Turkish (n = 3), did not have T2D (n = 8), or did not provide blood samples within the 3-month study period (n = 11). Interested participants were initially interviewed on the phone, at which time the study purpose was explained, and age and gender of the responders were recorded.

Physical exam

A research assistant (RA) fluent in both Dutch and Turkish languages interviewed participants in their preferred language. The RA assisted and completed questionnaires on age, education, gender, Islamic diet, marital status, parity, and prescription medication(s) use including diabetes medications and statins. Parity number was defined as the number of live childbirth (number of live birth) plus the number of stillbirth (defined as birth of an infant that died after the 20th week of pregnancy in the uterus).

Blood pressure (BP) was measured by clinical protocol using an automated sphygmomanometer with the participant resting alone in a quiet room. Measurements were performed twice and the average reading taken as the participant's BP. The BP readings were displayed in pairs, with the upper (systolic) value first, followed by the lower (diastolic) value. Waist circumference (WC) to the nearest 0.1 cm was measured horizontally with a non-stretchable measuring tape placed midway between the 12th rib and iliac crest at minimal respiration to measure central obesity. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2).

The Department of Phlebotomy at Haaglanden Medisch Centrum (HMC) Westeinde collected participants' serum samples during physical exams, aliquoted them, and kept them frozen at −20°C until they could be analysed. Venous blood (20 mL) was collected after an 8–12 h overnight fast, by a certified phlebotomist who used standard laboratory techniques. Serum measurements were performed at HMC hospital laboratory.

Independent variable: Cutoff of serum cotinine level (≥10 ng/mL)

Cotinine, the primary metabolite of nicotine, is a prognostic biomarker used to differentiate smokers from non-smokers in epidemiologic studies. Because of its longer half-life, cotinine, measured in serum, urine, or saliva, allows for differentiating active smokers from passive and non-smokers (24). According to the Centers for Disease Control and Prevention (CDC)–National Biomonitoring Programme (25), non-smokers exposed to SHS have serum cotinine levels <1 ng/mL, with high SHS exposure yielding values in the 1–10 ng/mL range. High serum cotinine levels (≥10 ng/mL) indicate active smokers. Serum cotinine was measured with a solid-phase competitive chemiluminescent immunoassay.

Dependent variables: Lipid/lipoprotein-related indices

Diabetic dyslipidaemia is commonly illustrated by high CHOL, low HDL-c, high TG, and high LDL-c (26). It is widely recognised that these lipid variations characterise the major association between T2D and increased cardiovascular risk of diabetic patients. Smoking has also been shown to alter lipid/lipoprotein levels (18). Serum lipids and lipoproteins were determined by enzymatic *in vitro* assay and included: CHOL, HDL-c, LDL-c, and TG.

CVD risk measurements

The Castelli risk index-I (CRI-I), also known as cardiac risk ratio (CRR), suggests the development of coronary plaques with a diagnostic value as good as the determination of CHOL (27). The CRI-I was calculated by the standardised formula: CRI-I = CHOL/HDL-c. The scientific literature report that in an effort to enhance the predictive capacity of lipid-related indices, several lipoprotein ratios or "atherogenic indices" have been defined. The atherogenic coefficient (AC) is a significant index that can be used as a stand-alone index for CVD risk estimation (28). The AC was calculated by the standardised formula: AC = (CHOL–HDL-c)/HDL-c.

Covariates

To control for potential confounding between serum cotinine level and lipid-related indices, after reviewing several related studies and based on clinical significance of factors that affect the independent and/or dependent variables (18), we included the following covariates in the analysis- age (years), gender (male or female), waist circumference, education (some school or high school graduate or above), diabetes medications (yes or no), and statins (yes or no). It has been established that there are differences in lipids by gender and age. Percent of fat, of which WC is a proxy variable, is associated with lipids and lipid markers. We therefore included WC,

instead of BMI, since it is proven to be a better indicator of body fat around the visceral organs which is associated with metabolic complications. The aforementioned covariates are also associated with glycated haemoglobin (HbA1c) values, which is clinically considered to be the gold standard for monitoring glycaemic control in patients with T2D. All the above information was collected from face-to-face interviews or assessed during physical exams.

Statistical analyses

Serum cotinine level was analysed as a continuous variable. There were no missing values in the study sample (n = 110). Statistical analyses were performed on participants with complete data on all variables required for multiple linear regression (MLR) models. Differences between two categories of cotinine (high ≥10 ng/mL and low <10 ng/mL) were assessed using the independent samples t-test for numerical values and the chi-square test for categorical variables. The dependent variables were checked for normal distribution using the Shapiro-Wilks Normality Test, and homogeneity of variance using the Breusch-Pagan/Cook-Weisberg test for heteroskedasticity. Log-transformation of HDL-c, TG, CRI-I, and AC values were performed to account for the skewed nature of the raw data. All dependent variables conform to homogenous variance (P < 0.10). We ran MLR models to calculate the mean change in CHOL, HDL-c [log], LDL-c, TG [log], CRI-I [log], and AC [log] separately, for high serum cotinine levels (≥10 ng/mL) as a continuous variable (n = 32). Participants with low serum cotinine levels (<10 ng/mL) had values of 0 ng/mL (n = 78). We therefore categorised high serum cotinine level into quartiles. We ran MLR models to calculate the mean change in CHOL, HDL-c [log], LDL-c, TG [log], CRI-I [log], and AC [log] for each higher serum cotinine level by taking the lowest category as the referent (10≥cotinine ≤199 ng/ml). All MLR models were adjusted for age, gender, WC, diabetes medications, and statins. Stata 10.1 (StataCorp LP, College Station, TX) was used for statistical analysis and P < 0.05 was considered significant.

Results

Table 1 presents the baseline characteristics of the study population, all of whom were physician-diagnosed with T2D. There were no missing values for the participants therefore none were excluded from analysis. The 110 participants that were included in the study had a mean age of 52.5 years [standard deviation (SD) = 9.21]. Among the 32 participants that had high cotinine levels (≥10 ng/mL), approximately half of them were female (46.9%), married (68.8%), completed some high school or above (90.6%), followed an Islamic diet (93.8%), had a BMI >30 kg/m^2 (59.4%), and were taking statins (53.1%). The 32 participants, with high cotinine levels (≥10 ng/mL), had a mean of 1.75 of parity, had a mean of 103.63 cm of waist circumference, a mean of 139.5 mmHg systolic blood pressure, a mean of 82.53 mmHg diastolic blood pressure, a mean of 4.99 mmol/L CHOL, a mean of 0.08 mmol/L HDL-c [log], a mean of 3.09 mmol/L LDL-c, a mean of 0.56 mmol/L TG [log], a mean of 1.49 CRI-I [log], a mean of 1.21 AC [log], and a mean of 51.75 mmol/L HbA1c. Education, HDL-c [log], CRI-I [log], and AC [log] were statistically significant with high cotinine levels (≥10 ng/mL): P = 0.02, P = 0.04, P = 0.02, and P = 0.02, respectively.

TABLE 1 Baseline characteristics of study participants by serum cotinine cutoff of ≥10 ng/mL.

Variables	Cotinine (ng/mL)		
	High[a] (n = 32)	low[b] (n = 78)	P
Age (years)	50.66 ± 7.38	53.96 ± 9.74	0.09
Gender (F) (%)	46.88	62.82	0.12
Marital status (Yes) (%)	68.75	78.21	0.3
Education (Yes) (%)	90.63	69.23	**0.02***
Parity	1.75 ± 2	2.71 ± 2.47	0.05
Islamic diet (Yes) (%)	93.75	87.18	0.32
BMI (>30 kg/m2) (%)	59.38	67.95	0.39
WC (cm)	103.63 ± 9.36	105.60 ± 10.93	0.37
HbAlc (mmol/L)	51.75 ± 14.35	51.73 ± 14.94	0.99
SBP (mmHg)	139.5 ± 23.96	142.58 ± 20.23	0.49
DBP (mmHg)	82.53 ± 9.27	82.92 ± 10.28	0.85
CHOL (mmol/L)	4.99 ± 1.24	4.75 ± 1.12	0.32
HDL-c (mmol/L) [Log]	0.08 ± 0.27	0.2 ± 0.27	**0.04***
LDL-c (mmol/L)	3.00 ± 1.08	2.73 ± 0.94	0.08
TG (mmol/L) [log]	0.57 ± 0.45	0.49 ± 0.51	0.48
CRI-I [log]	1.49 ± 0.34	1.33 ± 0.32	**0.02***
AC [log]	1.22 ± 0.45	1 ± 0.47	**0.02***
Statins (yes) (%)	53.13	50	0.77

Data are means ± SD unless otherwise indicated.
*P is considered significant at <0.05. Bolded values mean statistically significant results.
[a]High cotinine is defined as ≥10 ng/mL. Level for cotinine (≥10 ng/mL) were considered reliable indicators for cigarette smoke.
[b]Low cotinine is defined as <10 ng/mL. Level for cotinine (<10 ng/mL) were considered reliable indicators for nonsmokers.
AC, atherogenic coefficient; BMI, body mass index; CHOL, total cholesterol; CRI-I, Castelli risk index-I; DBP, diastolic blood pressure; HbAlc, glycated haemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, Triglycerides; WC, waist circumference.

Parity had a weak association with high cotinine levels (P = 0.05). The geometric mean of serum cotinine level was 236.63 ng/mL [confidence interval (CI) = 175.89 ± 318.36].

Table 2 presents the association between serum cotinine (≥10 ng/mL) as a continuous variable and CHOL, HDL-c [log], LDL-c, TG [log], CRI-I [log], and AC [log] separately. Serum cotinine was positively associated with HDL-c [log] (P = 0.04), CRI-I [log] (P = 0.03), and AC [log] (P = 0.03) in the age, gender, waist circumference, diabetes medications, and statins-adjusted models. In contrast, there was no association between serum cotinine (as a continuous variable) and CHOL, LDL-c, and TG [log].

Table 3 presents the association between increasing quartiles of serum cotinine (≥10 ng/mL) and mean change in CHOL, HDL-c [log], LDL-c, TG [log], CRI-I [log], and AC [log], taking the lowest quartile of serum cotinine as the referent category (10 ≥cotinine ≤ 199 ng/ml). There was no association between increasing quartiles of serum cotinine and lipid-related indices. MLR indicated that there is some evidence for an effect, albeit rather weak evidence, for CRI-I [log] and AC [log] with p-values of 0.06 for both indices. We considered the conventional p-value of less than 0.05 to be statistically significant for all analyses, however, we reported the effect size and the 95% CI for each quartile. MLR results showed that participants in the

TABLE 2 Multiple linear regression analyses of the associations between serum cotinine (≥10 ng/mL) and lipid-related indices.

Dependent variables	Independent variable cotinine levels (≥10 ng/mL)[a] n = 32				
	β	SE	P	R^2	f^2
CHOL[b]	0.001	0.002	0.40	0.12	–
HDL-c[b] [log]	−0.001	0	**0.04***	0.39	0.65**
LDL-c[b]	0.002	0.001	0.29	0.17	–
TG[b] [log]	0	0.001	0.48	0.27	–
CRI-I[b] [log]	0.001	0	**0.03***	0.38	0.62**
AC[b] [log]	0.001	0.001	**0.03***	0.39	0.64**

*P is considered significant at <0.05. Bolded values mean statistically significant results.
[a]Level for cotinine (≥10 ng/mL) were considered reliable indicators for cigarette smoke.
[b]Dependent variables in separate multiple linear regression equations with covariates including age, diabetes medications, gender, statins, and waist circumference.
AC, atherogenic coefficient; β, regression coefficient; CHOL, total cholesterol; CRI-I, Castelli risk index-I; f^2, Cohen's effect size; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; R^2, coefficient of determination; SE, standard error, TG, Triglycerides.
**$f^2 = R^2/1\text{-}R^2$ calculated for significant regression models.

4th quartile (highest) of serum cotinine level, compared with those in the 1st quantile (lowest), had higher CRI-I (β = 0.35, 95% CI = −0.01, 0.72), and AC (β = 0.45, 95% CI = −0.02, 0.93) values. Participants in the 3rd quartile, compared with those in the 1st quartile, had higher CRI-I (β = 0.12, 95% CI = −0.23, 0.47) and AC (β = 0.16, 95% CI = −0.29, 0.62) values. Participants in the 2nd quartile, compared with those in the 1st quartile, had higher CRI-I (β = −0.02, 95% CI = −0.40, 0.35) and AC (β = −0.05, 95% CI = −0.54, 0.44).

Discussion

Cigarette smoking is associated with several CVDs, including atherosclerosis, heart failure, and stroke all of which result in damage to the heart and blood vessels. Active smoking may result in anatomical and biochemical changes to the coronary arteries and the myocardium, consequently leading to CVD. Examining a variety of diagnostic biomarkers that potentially assesses changes to components of the cardiovascular system may be beneficial in CVD management. Cigarette smoke contains nicotine in considerable concentration. Cotinine, a major metabolite of nicotine, is a specific and highly representative parameter for exposure to cigarette smoke. The chronic effects of cotinine on the cardiovascular system include unfavourable effects on specific lipoprotein levels, which play a role in the initiation of CVD (29). Based on findings of this study, it is suggested that serum cotinine be added to the standard of care for T2D management as it may provide important insights to lipid abnormalities and CVD risk among Turkish immigrants with T2D.

The present study showed that lipid ratios of HDL-c, CRI-I, and AC are positively associated with serum cotinine levels (≥10 ng/mL). These findings corroborate other studies where there is a significant association in HDL-c levels in smokers than in non-smokers and an association between inhaled cigarette smoke and the atherosclerotic risk (27, 30, 31). Our study evaluated lipid ratios of CRI-I and AC since these atherogenic indices are validated parameters associated with increased CVD risk. A cross-sectional study with 699 participants indicated that CRI-I predict the highest prevalence of predisposition to CVD risk (47.8%) (27). The Castelli risk index-II (CRI-II), atherogenic index of plasma (AIP), and CHOLIndex have been proposed as new lipid parameters in assessing CVD risk (27, 32). Olamoyegun et al. (27) reported that the AC, CRI-II, CHOLIndex, and AIP predicted a CVD risk prevalence of 22.5, 15.9, 11.2, and 11.0%, respectively. Some research suggest that alternative lipid-related indices be used to evaluate CVD risk even when serum lipid levels seem normal (32). According to the Framingham Heart Study (30), smokers who quit for more than 1 year have blood cholesterol levels similar to non-smokers. Garrison et al. (30) suggest that for males, a CRI-I of 5 signifies average risk for CVD. Whereas, females tend to have higher HDL-c levels; therefore, a ratio of 4.4 signifies average risk. This suggests that a high level of CHOL may be less alarming if the CRI-I ratio is low. Interestingly,

TABLE 3 The associations of quartile of serum cotinine level (Reference: 10 ≥ cotinine ≤ 199 ng/ml) with lipid-related indices[a].

Dependent variables	Quartile 1 (n = 8) 10 ≥ cotinine ≤ 199 ng/ml	Quartile 2 (n = 8) 200 ≥ cotinine ≤ 324 ng/ml	Quartile 3 (n = 8) 325 ≥ cotinine ≤ 455 ng/ml	Quartile 4 (n = 8) 456 ≥ cotinine
CHOL[a]	Reference	β = −0.74, 95% CI = −2.32, 0.84 (0.34)	β = −0.24, 95% CI = −1.71, 1.24 (0.74)	β = 0.59, 95% CI = −0.94, 2.11 (0.43)
HDL-c [log][a]	Reference	β = −0.14, 95% CI = −0.45, 0.17 (0.37)	β = −0.19, 95% CI = −0.48, 0.10 (0.19)	β = −0.23, 95% CI = −0.53, 0.07 (0.12)
LDL-c[a]	Reference	β = −0.48, 95% CI = −1.86, 0.90 (0.48)	β = 0.07, 95% CI = −1.22, 1.36 (0.91)	β = 0.53, 95% CI = −0.80, 1.86 (0.42)
TG [log][a]	Reference	β = −0.27, 95% CI = −0.77, 0.22 (0.27)	β = −0.16, 95% CI = −0.62, 0.31 (0.49)	β = 0.23, 95% CI = −0.25, 0.71 (0.33)
CRI-I [log][a]	Reference	β = −0.02, 95% CI = −0.40, 0.35 (0.89)	β = 0.12, 95% CI = −0.23, 0.47 (0.49)	β = 0.35, 95% CI = −0.01, 0.72 (0.06)
AC [log][a]	Reference	β = −0.05, 95% CI = −0.54, 0.44 (0.82)	β = 0.16, 95% CI = −0.29, 0.62 (0.47)	β = 0.45, 95% CI = −0.02, 0.93 (0.06)

[a]Dependent variables in separate multiple linear regression equations with covariates including age, diabetes medications, gender, statins, and waist circumference.
AC, atherogenic coefficient; β, regression coefficient; CHOL, total cholesterol; CI, confidence interval; CRI-I, Castelli risk index-I; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TG, Triglycerides.

studies have shown that Turkish immigrants tend to have a lower prevalence of high CHOL levels, a known risk factor for CVD, as compared to the native Dutch (9, 13, 14, 17, 33). Results of our study are corroborated by previous studies that showed low CHOL levels among the Turkish immigrant population, regardless of statin use.

Patients with T2D are more prone to dyslipidaemia, a major risk factor for CVD in T2D. Diabetes-induced dyslipidaemia may be manifested by reduced HDL-c, increased LDL-c, and increased TG levels in the blood (11, 34). In patients with diabetic dyslipidaemia, statin therapy has beneficial effects to cardiovascular health (11). However, other than decreasing the LDL-c levels, the management of dyslipidaemia in patients with T2D continues to be challenging (35). Another factor that may increase risk of dyslipidaemia includes cigarette smoking. Reiss et al. (36) conducted a systematic review to examine the smoking prevalence among immigrant population from non-Western and Western countries. The majority of the studies (23 of 27) reported a strong association between gender and smoking behaviour. Socio-demographic factors including age, gender, and education are known to determine smoking behaviour across all population groups. Nierkens et al. (15) investigated the smoking prevalence among three immigrant populations in the Netherlands and results show that the prevalence of smoking was highest among the Turkish, with 63% of Turkish males who smoke and 32% of Turkish females who smoke. Additionally, the youngest immigrant population (34–44 years) had higher smoking rates as compared to the older age group (45–60 years). Educational level in relation to smoking behaviour have been examined in several studies and results show that Turkish males with a lower education and Turkish females with a higher education tend to have higher smoking rates (13, 15). Our study revealed that education was significantly associated with high serum cotinine levels ($P = 0.02$).

There is a high prevalence of smoking among Turkish in country of origin (Türkiye) and host country (Netherlands) (36). Cultural perceptions of smokers among Turkish immigrants warrant further investigation as the high rate of smokers may be influenced by cultural practices (13, 37). Furthermore, environmental determinants of smoking including living in deprived neighbourhoods and socioeconomic status (SES) are known to adversely impact health (15, 17, 22). Middelkoop et al. (38) characterised The Hague by the largest variation in neighbourhood deprivation scores and highest level of segregation in the Netherlands. Mortality data of residents, under the age of 65 years, show that CVD was responsible for cause of death among 32.5% males and 21.3% females living in The Hague (38). Data indicate that mortality risk increased in deprived neighbourhoods, and a strong association between deprivation score and percentage of non-Western inhabitants. A recent study conducted in the Netherlands emphasises the importance of GP awareness to reach smokers in deprived neighbourhoods (22). The prevalence of GP healthcare services is generally observed to be much higher among Turkish in the Netherlands (9, 13). Turkish tend to report more complaints to the GP, are more likely to seek advice from a specialist, and have high hospital-admission rates with regards to heart complaints (13). In our study, the majority of participants (54.5%) were recruited from GP offices. Based on previous studies, it is suggested that GPs may play an important role in effective T2D management (39–42). Health professionals are encouraged to develop ethnically targetted interventions in the Netherlands (17, 33, 36, 39, 43–45). Approximately 10% of the population in the Netherlands are non-Western immigrants, which is expected to increase to 20% by 2060 (43). Interestingly, non-Western immigrants have a lower average SES than the native Dutch population (43). The health effects of SES are determined by several risk factors including physical living (neighbourhood deprivation) and health-related behaviour (cigarette smoking). Effective preventive and treatment approaches to T2D management among Turkish immigrants may decrease the burden of ethnic inequalities in health (33, 39, 45). Ethnic-specific data could help GPs assess which indicators to be added to the standard of care.

This study examined first-generation Turkish immigrants with T2D living in a deprived neighbourhood of The Hague, Netherlands. Turkish form the largest first-generation immigrant group in the Netherlands, with a large population living in the most deprived neighbourhoods (14, 17). Research has shown that ethnic minority groups are less likely to participate in research studies, possibly due to language barrier and low literacy. Despite limitations such as these, this study adds to the scarce research in a poorly represented group. It is suggested that non-Western immigrants may import their smoking behaviour from the country of origin to the host country. However, Reiss et al. (46) report that immigrants themselves could potentially influence the majority population's health behaviour. Environmental stressors including living in deprived areas may also increase smoking behaviour. A longitudinal study conducted in the Netherlands indicates a causal relationship between neighbourhood deprivation and smoking status (47). The authors conclude that the socioeconomic characteristics of areas in which smokers reside impact their quitting behaviour. According to the CDC–Office on Smoking and Health (48), several studies suggest an association between cigarette smoking and low SES. The 2015 CDC Morbidity and Mortality Weekly Report (49) states that low SES populations are at an increased risk of SHS exposure and therefore prone to being affected from the harmful effect of cigarette smoke. In the aforementioned study, SHS exposure was determined using serum cotinine; the primary metabolite of nicotine. The CDC–National Biomonitoring Programme (25) currently recommends cotinine as the best biomarker of ascertaining nicotine exposure.

In large nationally representative samples of US adults (NHANES 2003–2012), higher serum cotinine levels are associated with risk of developing diabetes among never smokers exposed to SHS (50). Additionally, previous studies consistently show that risk factors including T2D, cigarette smoking, and dyslipidaemia are associated with CVD morbidity and mortality (10–12, 51). Lifestyle modification including smoking cessation could potentially provide some benefit in high-risk populations with diabetes-induced dyslipidaemia. To the best of our knowledge, this is the first study to examine the association of serum cotinine and lipid-related indices among first-generation (foreign born) Turkish immigrants with T2D living in deprived neighbourhoods of The Hague, Netherlands. Diabetes-induced dyslipidaemia is a known risk factor for CVD; therefore, examining modifiable risk factors such as cigarette smoke could provide important insights into the possible role of successful T2D management. This study demonstrated that cigarette smoke, based on serum cotinine $\geq$10 ng/mL, had a negative effect on specific lipid-related ratios. Cotinine is the main metabolite of nicotine. and preferred biomarker in clinical studies, since it is not affected by the environment or diet, thus completing requirements of specificity and half-life in the body (52). Raja et al. (53) reported that serum cotinine has a longer half-life, as compared to salivary cotinine, and does not need adjusting for hydration difference among individuals as in saliva testing. A prospective study done in the Netherlands concluded that serum cotinine showed greater stability than urinary cotinine

and is therefore more practical for use in clinical settings (54). The scientific literature report varying cut-off points for serum cotinine levels (25, 50). The Society for Research on Nicotine and Tobacco (SRNT) Subcommittee on Biochemical Verification (55), report that cotinine levels range from 10 to 20 ng/ml due to variability in diverse racial groups. We determined a serum cotinine cut-off value of ≥10 ng/mL to be an indicator of active smoking, as recommended by the CDC–National Biomonitoring Programme (25).

Wakabayashi (31) found that in patients with diabetes, the levels of lipid-related indices were higher in smokers than in non-smokers, which plays a major role in the development of atherosclerotic CVD. While the prevalence of smoking is high in Turkish immigrants (13–15), few studies have examined the effect of serum cotinine and its role in T2D and CVD in this high-risk population. Dyslipidaemia coupled with T2D and cigarette smoking could potentially lead to the high CVD prevalence observed among Turkish immigrants living in the Netherlands. An observational study done in Türkiye among 307 patients who underwent diagnostic coronary angiography found the CHOLIndex to have an independent predictive value for CVD (OR = 1.011, P = 0.009) (32). Akpınar et al. (32) indicated that age, diabetes status, male gender, and cigarette smoking were independent predictors of CVD. Furthermore, the authors suggest the CHOLIndex appropriate when evaluating lipid-related risk for CVD. Alternative ethnic-specific lipid and lipoprotein parameters should be investigated in larger cohorts with T2D to assess the association of serum cotinine, as an indicator of active and passive cigarette smoke exposure, and CVD risk.

The high prevalence of smoking among Turkish immigrants in the Netherlands poses a major public health concern. Smoking habits of active smokers could potentially endanger others to SHS. Recent data from large nationally representative samples of US adults show an association between higher serum cotinine levels and associated diabetes among never smokers (50). Additionally, Jain and Ducatman's study (18) concluded that serum cotinine was significantly associated with unfavourable lipid/lipoprotein profiles among the adult population of the USA. Modification of lifestyle risk factors that includes prevention of cigarette smoke could potentially lessen CVD risk in Turkish immigrants with and without T2D. A comparative analysis of 6,517 Turkish immigrants showed a higher smoking prevalence among Turkish immigrants in the Netherlands than among their counterparts in Germany (46). Data from the LASER study reported the highest prevalence of smoking in first-generation Turkish males (54.9%) as compared to second-generation Turkish males (45.6%) and native Dutch males (36.2%) (16).

The high prevalence of T2D among Turkish immigrants in the Netherlands remains unclear. There is a much higher rate of T2D observed in Türkiye when compared to the Netherlands (9). Studies indicate that the diets of non-Western immigrants differ from that of the native Dutch (13, 56). van Leest et al. (13) report that Turkish immigrants tend to eat more fruits and vegetables. However, there is a high prevalence of overweight and obesity among first-generation Turkish immigrants in the Netherlands (20). Physical activity should also be considered when assessing serum levels. Research shows that Turkish immigrants are less likely to be physically inactive, especially first-generation immigrants (≈10%) (13). Genetics also plays an important role in the low levels of HDL-c typically observed among the Turkish population (29). Clinical practice guidelines and adherence for T2D management in Dutch GP offices can be challenging (40, 42). The 2013 NHG standard for T2D and 2012 NHG standard for CVD risk management recommend that patients with modifiable risk factors, should be given the following lifestyle advice to reduce the risk of CVD: no smoking, optimal physical activity, healthy diet, optimum weight, and avoidance of stress (41, 42).

The pathogenesis of CVD in T2D is multifactorial and cigarette smoking and dyslipidaemia are known to be powerful independent risk factors. The detrimental health effects of cigarette smoke are well documented and have been linked to many chronic diseases. The 2014 Surgeon General's Report on smoking and health, states that smoking is a major cause of CVD and causes one of every three deaths from CVD (57). Additionally, the relationship between carbohydrates and lipid metabolism in patients with T2D may be affected by various factors. High-risk populations with T2D are more prone to dyslipidaemia since insulin resistance disrupts important enzymes and pathways in lipid metabolism. Numerous studies indicate that lipid-related indices are good indicators to assess CVD risk in patients with T2D (27, 30–32). Among the indices examined, results of this study show that cigarette smoke as defined by high serum cotinine levels has better predictability to assess lipid ratios of HLD-c, CRI-I, and AC in Turkish immigrants with T2D living in deprived neighbourhoods of The Hague, Netherlands. However, there is a need for additional lipid-related indices to be measured in larger cohorts that include prospective studies to assess serum cotinine levels and CVD in high-risk populations with diabetes and lipid irregularities.

Strengths and limitations

This study adds to the body of research on serum cotinine, as an indicator for cigarette smoke, and lipid irregularities in high-risk populations with T2D. de Weerd et al. (54) suggest serum cotinine to be a more reliable measure, as opposed to urinary cotinine, for use in clinical settings. A major strength of this study is that serum cotinine was examined to minimise the potential for misclassification of smoking status and to emphasise biochemical confirmation of cigarette smoke. The participants were asked not to change their smoking behaviours on the day of blood collection. Participants included are all of Turkish descent, a single origin, in which research concerning serum cotinine and lipid abnormalities in T2D are limited. Turkish immigrants were examined because of the high prevalence of CVD, cigarette smoking, and T2D when compared to the native Dutch (9, 13–15). We used standardised protocols, including uniform anthropometric and biochemical measurements in a clinical setting. We adjusted the statistical analysis for all major confounders of cotinine and lipids including age, gender, WC, diabetes medications, and statins. One strength of this study is that due to the availability of Turkish-speaking staff, also those first-generation Turkish immigrants who cannot read or write, and are not able to understand or speak Dutch, were included. Our study investigates modifiable health-risk behaviours, such as cigarette smoking, in a vulnerable population living in deprived neighbourhoods of The Hague, Netherlands. Neighbourhood characteristics affect ethnic inequalities in health, an area where more research is needed to confirm our preliminary findings. Another major strength of this study is that our cross-sectional design was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)-guidelines (58).

There are a number of potential limitations in this study. Due to the study's cross-sectional nature, our results do not establish causality and cannot be generalised to other populations. Several

studies indicate that metformin and statins significantly reduce CHOL, LDL-c, and TG, and increase HDL-c levels. Additional statistical analyses were done to determine the potential confounding effect of diabetes medications and statins. Results of these tests verified that the direction did not change. All MLR models (**Tables 2**, **3**) were adjusted for the aforementioned covariates. Further statistical analyses were done to determine the potential effect size and the 95% CI for each quartile of higher serum cotinine level by taking the lowest category as the referent (10 ≥cotinine ≤199 ng/ml). Our findings did not indicate a significant association between increasing quartiles of serum cotinine and lipid-related indices.

Although serum cotinine and lipid levels are ethnically specific, our sample was not randomly selected and may not represent the Turkish immigrant population of the Netherlands. Longitudinal studies are recommended to determine the effect of serum cotinine on lipid-related indices and consequent CVD morbidity and mortality in Turkish immigrants with T2D. The study sample size (n = 110) also warrants further investigation in larger cohorts. However, the sample size of our study is comparable to other studies in the Netherlands (17, 22, 43, 44). El Fakiri et al. (17) investigated the prevalence of cardiovascular risk factors among various ethnic groups at high risk of developing CVD within GP offices in the Netherlands. The researchers analysed data on 126 Turkish patients, among other ethnic groups (17). Benson et al. (22) investigated smoking cessation behavioural therapy among 59 ethnic minorities, including Turkish, living in disadvantaged neighbourhoods of the Netherlands. Schouten et al. (44) analysed data of the Rotterdam Intercultural Communication in Medical Settings (RICIM) project, in which patients of 38 GP offices with a multi-ethnic population participated. The RICIM dataset investigated 103 patients (56 patients belonging to one of the major ethnic minority groups in the Netherlands—Turkish, Moroccan, Surinamese, Antillean, Cape Verdian—and 47 Dutch patients). Our research study collected data within a 3-month period from a high-risk first-generation Turkish immigrant population living in a deprived neighbourhood of The Hague, Netherlands, where research is limited. Recruitment methods support other studies that indicate that GPs are most effective in reaching the immigrant population, specifically when recruiting smokers living in disadvantaged areas (59–61).

Conclusion

This cross-sectional study identifies the compelling need to investigate several important clinical and public health concerns related to smoking and unfavourable lipid/lipoprotein profiles in Turkish immigrants with T2D, preferably by well-designed longitudinal prospective studies and randomised clinical trials. It is well-known that T2D is a multidimensional disorder and there is an increasing need to address the biomedical root causes of CVD risk and the adverse effect induced by lipid/lipoprotein markers. These should be looked at as aetiological causes of CVD risk in patients with T2D. Additionally, the pathogenesis of T2D and CVD are associated with elevated lipid/lipoprotein markers such as CHOL, LDL-c, HDL-c, and TG (18). The present study indicates that lipid ratios of HDL-c [log], CRI-I [log], and AC [log] are dependent determinants of serum cotinine and higher serum cotinine levels (≥10 ng/mL) are associated with worse HDL-c [log], CRI-I [log], and AC [log] values in participants with T2D. Clinical comprehension of these biochemical indicators (lipids/lipoproteins) and symptomatic results (CVD risk) in patients with T2D will aid in the intervention (smoking) approach for this vulnerable cohort (Turkish immigrants).

Smoking is a preventable risk factor for CVD and public health awareness of its adverse effects in individuals with T2D should be promoted among high-risk populations. Prevention and decrease of cigarette smoke in Turkish immigrants with T2D may help protect their cardiovascular health and decrease CVD risk. Adding serum cotinine testing to the standard of care for T2D may direct management in the primary prevention of CVD among first-generation Turkish immigrants. There is a need for vulnerable groups living in deprived neighbourhoods to be further educated on effective T2D self-management. Therapy that is targetted to modify this behavioural risk factor may improve cardiovascular health outcomes and prevent comorbidities in Turkish immigrants living in deprived neighbourhoods in the Netherlands. In the meantime, this report contributes to a growing body of information and provides essential guidance to researchers and clinicians.

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 (1) Central Committee on Research Involving Human Subjects; (2) Florida International University Institutional Review Board (project identification code: 111210-01, date of approval: 12 February 2010). Informed consent was obtained from all individual participants included in the study. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SS designed and coordinated the study, participated in data collection and analysis, and drafted the manuscript. GZ prepared the original data files, performed the data analysis, and was involved in critical revision of the manuscript. LS contributed to the design of the study and critical revision of the manuscript. JV contributed to the interpretation of the data and helped to bring the manuscript to its final version. AS contributed to the acquisition and interpretation of data and helped to finalize the manuscript. FH contributed to the design and coordination of the study and critically revised the manuscript. All authors read and approved the final manuscript.

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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

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Adherence to the therapeutic guidelines recommendations among the people with type 2 diabetes mellitus and obesity, frailty, or recent diagnosis, attended in primary health care centers in Spain: A cross-sectional study

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Introduction: Clinical practice guidelines are helpful for clinicians, and their proper implementation could improve the quality of care and management of participants with diabetes. This study aimed to evaluate the degree of adherence to the Clinical Practice Guidelines (CPG) recommendations among obese, frail, or recently diagnosed type 2 diabetes mellitus (T2DM) participants in primary care centers in Spain.

Methods: We perform a cross-sectional study on a national level in two phases. In the first phase, study participants were recruited, and their clinical data were collected. In the second phase, data related to the participating physicians were collected.

Results: In total, 882 participants from 240 physicians were analyzed. According to the study questionnaire, most participants from all three clinical groups had adequate adherence to the CPG. This percentage was highest among the recently diagnosed T2DM (91.6%) and lowest percent of frail T2DM persons (74.7%). The inadequate adherence to the guidelines was observed mainly among the obese and frail participants with T2DM from medical doctors with low CPG knowledge (3.4% and 3.5%, respectively). Regarding the patient's characteristics and degree of adherence to the guidelines, the participants with inadequate adherence were generally older, with higher BMI, poorer HbA1c control, and fewer visits with primary care physicians. Most (57%) primary care physicians had moderate CPG knowledge. In our multivariable logistic model, we did not

observe statistically significant odds ratios for different characteristics related to the physicians/consultation and low CPG knowledge.

Discussion: The results of our cross-sectional study observe adequate adherence to the clinical guidelines by the primary care physicians for the majority of the participants with obesity, frailty, or newly diagnosed with T2DM.

KEYWORDS

clinical guideline adherence, primary care (PC), Spain, type 2 diabetes, antidiabetic drug

1. Introduction

Type 2 diabetes mellitus (T2DM) is a highly prevalent chronic disease where proper control plays an important role in preventing damage to multiple organs or tissues. According to the International Diabetes Federation, it is expected that 1 in 10 adults will be affected by this disease until the year 2045 worldwide, when an especially high prevalence is expected among the population over 65 years of age (1). Currently, in Spain, the prevalence of T2DM is among the highest in Europe, with 14.8% (∼5.1 million adults) and an incredible increase of 42% just in 2 years since 2019 (2).

Poor metabolic control is associated with increased complications and premature mortality and is the leading cause of blindness, renal replacement therapy (dialysis/transplantation), and non-traumatic amputations (3). Early and multifactorial treatment and interventions could delay the onset of complications and improve quality and life expectancy (4). The therapeutic approach to the disease should be multidisciplinary and include pharmacological and non-pharmacological strategies and measures for preventing comorbidities and long-term complications (5–7). According to the therapeutic guidelines, the pharmacological treatment should be established gradually in therapeutic steps and in an individualized manner, considering patient- factors, such as age, the presence of associated comorbidities, the degree of prior control, and the presence or absence of other concomitant diseases and treatments (5, 7, 8).

In recent years, the scientific and clinical evidence regarding diabetes treatment increased substantially. The growing number of diabetes treatments (behavioral interventions, pharmacological treatment, surgery) and increasing information about their benefits and risks offer more options for people with diabetes and their health providers. Only in Europe, from 2005 to 2017, the European Medicines Agency (EMA) approved 40 new drugs for treating diabetes (9). Evidence-based practice has evolved as a dominant way of practice, policy, management, and education within health services throughout the developed world. However, the vast amount of information could complicate the decision-making process for proper treatment selection. Clinical practice guidelines, and local clinical and therapeutic protocols, are documents that provide physicians with updated and structured information for better management of patients. Clinical and therapeutic guidelines are considered essential resources for planning, providing, evaluating, and improving the quality of healthcare services (10). The main aim of clinical guidelines is to improve and standardize the quality of care among patients. Although rigorous evaluations have shown that clinical practice guidelines can improve the quality of patient care in experimental settings (11), whether they achieve this goal in daily clinical practice is less clear. This issue could be since patients, clinicians, health providers/payers, and managers define quality differently, and current evidence on guideline effectiveness is incomplete.

Implementing clinical practice guidelines remains a significant challenge for health professionals. Evidence indicates that many patients do not receive adequate care and may even receive inadequate or potentially harmful care or therapy (12). The degree of therapeutic inertia in people with diabetes is high in our primary health care settings. In the recently reported analysis of Mata et al. on 301,144 people with diabetes, the authors found that antidiabetic treatments were not intensified in patients who were treated with two oral drugs, for 26.2% of people with HbA1c > 7% and 18.1% with HbA1c > 8%. Intensification with a third oral drug or insulin was performed with HbA1c of 8.7% and 9.4%, respectively (13). These results are similar to those found in the U.K., where treatment with oral antidiabetics or insulin with HbA1c of 9.1% and 9.7% took an average of 7 years to be intensified third antidiabetic drug (14). Another study in the U.K. evaluated adherence to the National Institute for Health and Care Excellence (NICE) guidelines for starting and continuing glucagon-like peptide 1 (GLP1) agonists in patients with T2DM. Only 25% of patients started GLP-1 receptor agonists as part of a NICE-recommended regimen (15). However, although health professionals can provide advice or recommendations about medications, food intake, and the effects of physical activity, the main factors determining the success, achievement, and maintenance of metabolic control are the patient's ability and willingness to self-management (16). In a qualitative study conducted by Berenguera et al. (17) in our primary care setting with poorly controlled T2DM patients, although disease control alone (self-management) should occur daily, it was often difficult due to family or financial reasons, lack of awareness, or lack of motivation.

Clinical practice guidelines are helpful for clinicians, and their proper implementation could improve the quality of care and management of participants with diabetes. However, as a clinical tool, the proper implementation and use should be evaluated to know their actual effect in the medical consultation. To the best of our knowledge, no studies have been conducted in our primary care settings to evaluate adherence to therapeutic guidelines for managing T2DM. The objective of this study was to evaluate the degree of adherence to the therapeutic recommendations of the Clinical Practice Guidelines (CPG) among participants with

obesity, frailty, or recently diagnosed with T2DM in primary care centers in Spain.

2. Patients and methods

2.1. Study design and data source

We perform a cross-sectional study on a national level involving physicians from different primary care centers in Spain. The study was realized in two phases. In the first phase, study participants were recruited, and their clinical data were collected. In the second phase, data related to the participating physicians were collected. A specific survey was done to evaluate the degree of knowledge of the therapeutic guidelines, their opinion, and therapeutic preferences. The first phase was realized from June 1st, 2020, till November 30th, 2020 (6 months), while during December 2020 (1 month), we realized the second phase. The study recruitment consisted of offering the study participants to possible candidates. If participants agreed to enter the study, it was obligatory to sign the informed consent before any study procedure was performed or study data were collected. Regarding the primary care physicians selection, medical doctors from different regions of Spain were invited to participate in the study. If they agreed, they were involved in the study. All study procedures and data collection were performed in a single study visit. A contract research organization externally monitored the study recruitment and data collection.

2.2. Definition of eligibility criteria

T2DM (diagnosed according to the ADA—American Diabetes Association criteria) subjects aged at least 30 years old and with signed informed consent were included in the study. In order to identify the three groups of subjects: obesity, frailty, or recently diagnosed T2DM. We defined different sets of additional study criteria for each group. The T2DM subjects with obesity were requested to have ages between 55 and 74 years, a body mass index (BMI) of more than 30 kg/m^2, a T2DM diabetes duration longer than 5 years, and treatment with at least one antidiabetic drug. The frail T2DM person had to be at least 75 years old, with a T2DM duration longer than 5 years, and on treatment with at least two antidiabetic drugs. The frailty was defined according to the local electronic medical registry. T2DM participants with a recent diagnosis were requested to have between 30 and 55 years, with <3 years of disease duration. These criteria were chosen to create more homogenate clinical profiles of the three groups of patients with T2DM. The three clinical groups were selected since they are most prevalent in primary healthcare settings (18, 19). All participants with other types of diabetes (type 1, secondary, gestational, other) and those with medical history in the primary healthcare center for <1 year were excluded. The participant selection sampling strategy was a convenient approach based on the availability and willingness of the participants who fulfilled the study criteria to participate.

2.3. Clinical practice guidelines

We evaluate the adherence to the different guidelines available and in force at the moment of realization of the study. Guidelines were classified into international, national, and local. The treatment recommendations for the three clinical groups of T2DM were compared among the guidelines. Only therapeutic recommendations that were similar among the different guidelines were considered to evaluate adherence and knowledge. Supplementary Table 1 shows the guidelines used in the evaluation of their adherence.

2.4. Definition of variables

During phase one, participant's inclusion visits, different sociodemographic and clinical variables were collected, such as age, sex, toxic habits, hypertension, hyperlipidemia, other clinically important diseases, concomitant treatment, laboratory parameters, BMI, and diabetes duration. For each group of participants (obese, frail, and recently diagnosed), antidiabetic treatment at the moment of inclusion was collected. Different pharmacologic groups of antidiabetic treatment were analyzed (metformin, sulfonylureas, glinides, thiazolidinedione-TZDs, dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium-glucose co-transporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) analogs, fast-acting insulin, slow-acting insulin, intermedia acting insulin and mix action insulin). Based on this information, the variable "degree of adherence to therapeutic guidelines" was created using a scoring system. If the prescribed antidiabetic treatment was not recommended (contraindicated) by the guidelines for the specific participant group, a negative score (−1) was assigned. If the prescribed antidiabetic treatment was the one without specific recommendations or contraindications by the guidelines, a score of "0" was assigned. If the T2DM guidelines recommended the prescribed treatment, a score of "1" was assigned. In the case of multiple antidiabetic treatments, the scores were summarized. If the person had an overall negative score, it was classified as "inadequate adherence to the CPG." If the overall scoring was 0 was classified as "average adherence to the CPG." If the overall score was one or more, it was classified as "adequate adherence to the CPG."

During phase two, we collected variables from professionals participating in the study, such as sex, if they have diabetes, professional experience, information related to the type of medical consultation, and indicators for the health care provided to participants with diabetes (number of participants with T2DM treated, T2DM visits and time per person). Moreover, the degree of knowledge related to CPG was also collected from professionals based on the specific questionnaire on recommendations from the therapeutic guidelines for the three types of T2DM participants. Three groups of "degree of CPG knowledge" were created based on the quartiles obtained from the correct answers to the questionnaire. Low CPG knowledge if the professional has an overall score of at least 9. Moderate CPG knowledge if the overall score was between 9 and 12. High CPG knowledge if the overall

score was more than 12. Supplementary Table 2 shows the different items used to evaluate the degree of CPG knowledge.

2.5. Statistical analysis

The descriptive analyzes of phase one were carried out in the population of evaluable subjects by T2DM groups: subjects with obesity, frailty, and recently diagnosed, carrying out the comparative analyzes between the groups. The quantitative variables were described with measures of centralization and dispersion (mean, median, SD-standard deviation). Absolute and relative frequencies are described as qualitative variables. In the comparative analysis, depending on the characteristics of the variables and the number of groups being compared, parametric tests were used for those continuous variables that meet the application conditions (for example, *t*-test, ANOVA, etc.) and the non-parametric ones (for example, Chi-square, Fisher, Kruskal-Wallis, etc.) for ordinal, categorical variables or those that do not meet said parametric criteria. The p-values < 0.05 were considered statistically significant. Multivariate analysis was performed to determine related factors with a low level of knowledge using logistic regression, showing the Odds Ratio (OR) and its corresponding 95% confidence interval. In the model, professionals with moderate and high knowledge were merged into one variable to create a dichotomous depending variable. Missing data were not imputed and were left as missing. The data were analyzed using SPSS v22.0.

3. Results

In total, 262 primary care physicians were invited to participate; from those, 240 could be evaluated and included in the analysis. The participating physicians screened about 891 patients; from those, eight did not meet the study criteria and were excluded from the analysis. Supplementary Figure 1 shows the study flowchart.

3.1. Characteristics of the participants with diabetes

Participants with obesity and recently diagnosed with T2DM were mainly males (64.5% and 63.9%, respectively), while we observed more females (50.5%) in the frail group. Regarding the toxic habits, among the recently diagnosed participants, we observed more current smokers and alcohol consumers. The comorbidity profile was worst among the frail participants with T2DM for hypertension, CKD, and cardiovascular disease. At the same time, among the obese subjects, hyperlipidemia and mental illnesses were more prevalent than in the rest of the groups. Regarding laboratory parameters, no clinically significant differences were observed for HbA1c among the three groups. A poorer lipid profile was observed among the participants with a recent diagnosis of T2DM, and a poorer renal profile among the frail participants. Participants in the obese group mainly used lipid-lowering drugs. The remaining concomitant treatments (antihypertensive, antiplatelet, and anticoagulant drugs) were mostly used in the frail group. Regarding the antidiabetic drugs, metformin, DPP-4i, and slow-acting insulins were mainly used by frail people, while participants in the obese group mainly used SGLT-2i and GLP1-RA. We observed differences among the three groups for the number of medical visits related to diabetes in the last 12 months with physicians and nurses. The participants with obesity and T2DM had the highest, while participants with a recent diagnosis of T2DM had the lowest average number of visits with the professionals (4.3 visits $\pm$3.9). The inadequate adherence to therapeutic guidelines was observed mainly among the participants in the obese and frail groups (3.4% and 3.5%, respectively). An average degree of adherence to the CPG was mainly observed among the participants in the frail group. In contrast, adequate adherence to the CPG was mostly observed among the newly diagnosed participants with T2DM. Table 1 summarizes the characteristics of the subjects included in the study.

3.2. Characteristics of the professionals

Most of the professionals (primary care physicians) included in the analysis were males. About 8.3% reported having T2DM. We observed that physicians included in our study had, on average, 26.4 years of professional experience, 16.7% were members of some diabetes working group, and 74.2% had some educational course related to diabetes in the last 12 months. The majority (69.2%) worked in urban primary health care centers; on average, 225.3 patients with T2DM in their consultation, and the average time for consultation per person with T2DM was 11.3 min. Stratified for the degree of knowledge, the majority, 137 (57%) of the primary care physicians, had a moderate degree of CPG knowledge based on the answers to the study questionnaire. Supplementary Table 2 shows the descriptive analysis of the answers to the study questionnaire used to estimate the degree of CPG knowledge. We did not observe statistically significant differences among the three degrees of CPG knowledge. However, the low-degree group had perceptually more males, on average 27.4 years of professional experience, and with more experience in participation in the clinical trial for diabetes and other metabolic/cardiovascular/renal diseases in the last 12 months. The professionals from this group were the majority from semi-urban primary care centers with the lowest number of patients in the quota and subjects with diabetes. Table 2 summarizes the characteristics of primary care physicians.

3.3. The degree of adherence to the CPGs in the three clinical situations

Stratifying the degree of adherence to the CPG and the professionals' CPG knowledge, we observed that inadequate adherence to the guidelines was mainly observed only among the obese and frail participants with diabetes from medical doctors with a low degree of CPG knowledge according to the study questionnaire. The average adherence to the CPG was mainly present among frail participants (61.0%) from professionals with moderate knowledge. Adequate adherence to the guidelines was mainly achieved among the recently diagnosed participants with

TABLE 1 Characteristics of the participants.

	Obese T2DM subjects $n = 296$	Frail T2DM subjects $n = 289$	Recently diagnosed T2DM subjects $n = 296$	*p*-value
Sociodemographic and toxic habits				
Age, mean (SD), years	63.0 (4.5)	79.8 (4.2)	49.0 (5.3)	<0.001*
Sex, *n* (%), male	191 (64.5)	143 (49.5)	189 (63.9)	<0.001**
Alcohol consumption^{+}, *n* (%)	63 (21.3)	34 (11.8)	80 (27.0)	<0.001**
Current Smoking, *n* (%)	59 (19.9)	23 (8.0)	90 (30.4)	<0.001**
Comorbidities, *n* (%)				
Hypertension	239 (80.7)	245 (84.8)	133 (44.9)	<0.001**
Hyperlipidemia	252 (85.1)	221 (76.5)	189 (63.9)	<0.001**
Cardiovascular disease	3 (1.0)	20 (6.9)	2 (0.7)	<0.001**
Chronic kidney disease	38 (12.8)	81 (28.0)	19 (6.4)	<0.001**
Relevant mental illness	38 (12.8)	51 (17.6)	39 (13.2)	0.184**
Clinical variables				
Diabetes duration (years)	11.2 (6.0)	15.1 (8.0)	1.8 (0.9)	<0.001*
BMI, mean, (SD)	33.4 (2.9)	29.7 (4.5)	29.8 (5.0)	<0.001*
Laboratory parameters				
HbA1c (%), mean, (SD)	7.4 (1.1)	7.4 (1.3)	7.3 (1.3)	0.037*
Triglycerides (mg/dL),mean, (SD)	177.7 (78.0)	159.1 (68.0)	177.5 (79.6)	0.002*
Cholesterol total (mg/dL),mean, (SD)	199.5 (44.4)	186.5 (45.3)	201.9 (43.1)	<0.001*
Cholesterol LDL (mg/dL),mean, (SD)	116.1 (40.2)	106.1 (36.8)	121.1 (36.2)	<0.001*
Glomerular filtration (mL/min/1.73 m^2), (SD)	76.8 (18.6)	68.2 (19.6)	84.0 (18.9)	<0.001*
Albumin/creatinine ratio (mg/dL),mean, (SD)	51.8 (184.4)	80.2 (305.1)	46.7 (223.8)	0.003*
Concomitant treatments, *n* (%)				
Antihypertensive drugs	237 (80.1)	244 (84.4)	132 (44.6)	<0.001**
Lipid-lowering drugs	250 (84.5)	220 (76.1)	177 (59.8)	<0.001**
Antiplatelet drugs	102 (34.5)	131 (45.3)	40 (13.5)	<0.001**
Anticoagulant drugs	14 (4.7)	36 (12.5)	10 (3.4)	<0.001**
Glucose lowering drugs, *n* (%)				
Metformin	217 (73.3)	230 (79.6)	228 (77.0)	0.196**
SU	18 (6.1)	36 (12.5)	17 (5.7)	0.004**
Glinides	11 (3.7)	34 (11.8)	9 (3.0)	<0.001**
TZDs	1 (0.3)	4 (1.4)	1(0.3)	0.296***
DPP-4i	185 (62.5)	224 (77.5)	139 (47.0)	<0.001**
SGLT-2i	95 (32.1)	68 (23.5)	76 (25.7)	0.052**
GLP1-RA	35 (11.8)	19 (6.6)	16 (5.4)	0.009**
Insulin fast acting	5 (1.7)	7 (2.4)	4 (1.4)	0.612**
Insulin slow acting	35 (11.8)	61 (21.1)	22 (7.4)	<0.001**
Insulin intermedia acting	0 (0.0)	6 (2.1)	0 (0.0)	0.001***
Insulin mix action	2 (0.7)	7 (2.4)	1 (0.3)	0.066**
Number of visits related to diabetes in the last 12 months, mean, (SD)				
Primary care physician	4.3 (3.9)	4.2 (3.3)	3.3 (2.6)	<0.001*

(Continued)

TABLE 1 (Continued)

	Obese T2DM subjects $n = 296$	Frail T2DM subjects $n = 289$	Recently diagnosed T2DM subjects $n = 296$	p-value
Primary care nurse	4.4 (5.7)	4.3 (4.0)	3.4 (3.4)	<0.001*
Adherence to therapeutic guidelines, *n* (%)				<0.001*
Inadequate	10 (3.4)	10 (3.5)	0 (0.0)	
Average	45 (15.2)	63 (21.8)	25 (8.4)	
Adequate	241 (81.4)	216 (74.7)	271 (91.6)	

BMI, body mass index; HbA1c, glycosylated hemoglobin; [+]Moderate and high-risk alcohol consumption; DPP-4i, dipeptidyl peptidase 4 (DPP-4) inhibitors; SGLT-2i, sodium-glucose co-transporter 2 (SGLT2) inhibitors; GLP1-RA, glucagon-like peptide-1 (GLP-1) analogs; TZDs, thiazolidinediones; T2DM, type 2 diabetes mellitus; SU, sulphonylureas; SD, standard deviation; NIAID, non-insulin antidiabetic drugs.
Statistical tests used: (*) Kruskal-Wallis, (**) Chi-square, (***) Fisher.

TABLE 2 Characteristics of the professionals and their degree of CPG knowledge.

	Total	Degree of CPG knowledge			
	Physicians $n = 240$	Low ($n = 61$)	Moderate ($n = 137$)	High ($n = 42$)	p-value
Sex, *n* (%), male	167 (69.6)	46 (75.4)	94 (68.6)	27 (64.3)	0.450**
Comorbidities, *n* (%)					
Type 2 diabetes presence	20 (8.3)	4 (6.6)	15 (10.9)	1 (2.4)	0.207***
Experience					
Years of professional experience, mean (SD)	26.4 (9.2)	27.4 (9.0)	26.6 (9.3)	24.5 (8.8)	0.167*
Years in the last job mean (SD)	14.6 (9.9)	14.5 (9.9)	14.8(10.0)	14.0 (9.9)	0.923*
Member of a diabetes working group	40 (16.7)	6 (9.8)	27 (19.7)	7 (16.7)	0.227**
Courses/professional education related to diabetes management in the last 12 months, *n* (%)	178 (74.2)	40 (65.6)	107 (78.1)	31 (73.8)	0.177**
Participation in clinical trials for diabetes and other metabolic/cardiovascular/renal diseases in the last 12 months, *n* (%)	59 (24.6)	18 (29.5)	32 (23.4)	9 (21.4)	0.567**
Place of work					
Urban	166 (69.2)	39 (63.9)	97 (70.8)	30 (71.4)	0.899**
Semi-urban	44 (18.3)	13 (21.3)	24 (17.5)	7 (16.7)	
Rural	30 (12.5)	9 (14.8)	16 (11.7)	5 (11.9)	
Patients in the quota, mean, (SD)	1644.4 (701.4)	1460.4 (587.9)	1751.8 (805.0)	1565.6 (342.5)	0.244*
Participants with diabetes in the quota mean (SD)	225.3 (180.7)	191.1 (133.2)	246.1 (211.8)	208.1 (110.9)	0.382*
Participants with T2DM who visit weekly mean (SD)	27.4 (39.3)	28.2 (43.4)	29.5 (42.6)	19.4 (11.6)	0.224*
Duration of T2DM consultation per person (min) mean, (SD)	11.3 (4.5)	11.2 (4.4)	11.6 (4.9)	10.5 (3.1)	0.603*

CPG, clinical practice guidelines; SD, standard deviation.
Statistical tests used: (*) Kruskal-Wallis, (**) Chi-square, (***) Fisher.

T2DM (58.5%), especially among the patients from professionals with a moderate degree of CPG knowledge.

Regarding the patient's characteristics and the degree of adherence to the guidelines, the participants with inadequate adherence to the guidelines were generally older, with higher BMI, poorer HbA1c control, and fewer visits with primary care physicians. The patients with average adherence to the guidelines had the lowest average BMI and HbA1c and a higher average number of visits with their medical doctor. The lowest average HbA1c was observed among the recently diagnosed T2DM subjects with average adherence to the CPG. We observed a higher percentage with proper HbA1c control (HbA1c < 7%) among the recently diagnosed T2DM individuals and professionals with adequate CPG knowledge. The highest average number of visits with the medical doctor was observed among the obese participants with T2DM with average adherence to the CPG.

Table 3 summarizes the results related to adherence with the CPGs in the three clinical situations.

3.4. Factors related to the low level of CPG knowledge among the professionals

In the multivariable analysis, considering different potential factors for a low level of CPG knowledge among the professionals, we did not observe any statistically significant odds ratios. Figure 1 and Supplementary Table 3 show the results of this analysis.

4. Discussion

The results of our cross-sectional analysis on the degree of adherence with the therapeutic recommendations of the CPG among obese, frail, and recently diagnosed T2DM subjects in primary care centers in Spain show adequate adherence for most participants. This percentage was highest among the recently diagnosed T2DM subjects.

Similar studies evaluating adherence to the CPG were done in other countries but with different methodologies and objectives, making comparing difficult with our study. For example, cohort study from Luxemburg with 21,068 T2DM subjects for the period between 2000 and 2006, the authors evaluate the adherence of physicians and patients to annual follow-up recommendations from international guidelines for T2DM subjects (20). The authors reported that 90% of the patients consulted more than four times their treating physician. In our study, the average number of visits annually with the treating physician was different for three groups of participants, the highest number of visits among subjects with obesity (4.3 visits) and the lowest among the subjects with recently diagnosed T2DM (3.3 visits). Notably, the number of visits was higher among the obese than the frail persons, whose clinical conditions are more changeable due to their clinical complexity. A study from rural northern Alberta, Canada had, aim to evaluate adherence with the local clinical guidelines for clinical indicators and therapeutic targets on 368 patients with T2DM. The authors reported that, on average, the clinical indicators were near the recommended clinical practice guideline targets (49.7% with HbA1C $<$ 7%) (21). Another similar study from Swiss evaluated adherence with the local clinical guidelines target criteria for good disease management of diabetes in 604 patients. The authors reported that 44% of the patients achieved the therapeutic target [HbA1c $<$ 7% (53 mmol/mol)]. At the same time, this percentage was higher (77%) for the target [HbA1c $<$ 8% (64 mmol/mol)]. Compared with our results, 38.7% of the participants with adequate adherence with CPG had achieved the target of HbA1c $<$ 7%, and 75.8% achieved the target of HbA1c $<$ 8%. On the other hand, in Greece, recently, one study was published evaluating the level of adoption and adherence to local T2DM therapeutic guidelines among 226 Greek physicians (22). The authors reported that among the investigated physicians, there was a high level of adaptation to the guidelines (92.2%). However, the authors reported a low adherence (26.1%) to CPG. In our study, most physicians (57.0%) had average knowledge of therapeutic guidelines. In our multivariable model, we did not observe any statistically significant odds ratios for different characteristics of the professionals, consultation size, and low levels of CPG knowledge. One study in the U.K. evaluated the medical consultation size with practice performance and quality of care. The authors reported similar quality of care between the practices with larger numbers of patients and those with fewer patients per doctor (23). A recently published cross-sectional study assessing factors involved in adherence to CPGs on T2DM diabetes among the 98 endocrinologists working in public hospitals from Spain reported that non-adherence to CPG was a multifactorial problem related with the existence of multiple CPGs, the therapeutic inertia, the lack of time, and the complexity of diabetes (24).

Antidiabetic drugs should be selected for most of the current CPG, considering the individual patient's clinical characteristics and glycemic objectives (25). In the case of obesity and T2DM, the Standards of Medical Care in Diabetes from the American Diabetes Association for 2022, for patients where the objective is weight reduction, recommends the use of pharmacological agents with evidence of weight loss, such as metformin, α-glucosidase inhibitors, SGLT-2i, GLP1-RA, and amylin mimetics (26). Compared with our results, most participants with T2DM and obesity were using metformin, and surprisingly in second place (62.5%) were using weight-neutral drugs such as DPP-4i. About 11.8% and 6.1% of the participants with obesity were using weight-increasing drugs (insulins or sulphonylureas, respectively).

Concerning older adults and frailty, the international guidelines recommend metformin as first-line treatment if no contraindications exist (advanced renal insufficiency, impaired hepatic function) or gastrointestinal side effects which could reduce appetite or provoke vitamin B12 deficiency (27). In our study, most of the participants in the frail group were on metformin, while in second place by the use were the DPP-4inhibitors. In general, if no contraindication exit, DPP-4 inhibitors are also recommended due to the few side effects and minimal risk of hypoglycemia. Slow-acting insulins were mainly prescribed to these subjects. Once-daily slow-acting (basal) insulin has a good safety profile and is often used in older adults (28). A recently published review on diabetes and frailty suggests that as patients with diabetes get older, it is recommended to simplification, switch, or de-escalate the antidiabetic treatment depending on the frailty or HbA1Cc levels (22). In general, avoiding treatments that could induce hypoglycemia, such as sulphonylureas and fast-acting insulins, is suggested. Among our frail participants, 12.5% used some sulphonylureas, and 2.4% used some fast-acting insulins.

Regarding patients with a recent diagnosis of T2DM, most guidelines recommend using metformin as a first-line treatment when glycemic objectives are not reached with no pharmacological measures (dietary changes or physical exercises). In our study, most of the participants in this group were using metformin. In the recent therapeutic local guidelines from the RedGDPS foundation in Spain, in the case of young or recently diagnosed T2DM participants, the recommendation for the therapeutic objective is HbA1c $<$ 6.5% in monotherapy or non-pharmacological treatment, avoiding drugs with a risk of hypoglycemia (29). Our study observed that the proportion of subjects on some antidiabetic treatment that could cause hypoglycemia, such as sulphonylureas or insulins, was lower among the three groups. Proper therapeutic management in these recently diagnosed patients is important,

TABLE 3 Degree of compliance to the guidelines stratified by professional's different degrees of knowledge and patients characteristics.

		Degree of adherence to the CPG											
		Inadequate				Average				Adequate			
		Overall $n = 20$	Obese $n = 10$	Frail $n = 10$	Recently diagnosed $n = 0$	Overall $n = 120$	Obese $n = 39$	Frail $n = 59$	Recently diagnosed $n = 22$	Overall $n = 685$	Obese $n = 227$	Frail $n = 205$	Recently diagnosed $n = 253$
Patients from professionals with different degrees of knowledge	Low ($n = 209$)	10 (50.0)	5 (50.0)	5 (50.0)	–	39 (32.5)	18 (46.2)	12 (20.3)	9 (40.9)	160 (23.4)	47 (20.7)	52 (25.4)	61 (24.1)
	Moderate ($n = 478$)	8 (40.0)	4 (40.0)	4 (40.0)	–	63 (52.5)	16 (41.0)	36 (61.0)	11 (50.0)	407 (59.4)	140 (61.7)	119 (58.0)	148 (58.5)
	High ($n = 138$)	2 (10.0)	1 (10.0)	1 (10.0)	–	18 (15.0)	5 (12.8)	11 (18.6)	2 (9.1)	118 (17.2)	40 (17.6)	34 (16.6)	44 (17.4)
Patient characteristics	Age, mean, (SD)	71.4 (7.0)	65.0 (2.9)	77.8 (2.1)	–	68.3 (12.5)	62.9 (4.4)	79.6 (4.5)	49.4 (3.6)	62.8 (13.5)	62.9 (4.6)	79.9 (4.2)	49.0 (5.4)
	Sex (male), *n* (%)	14 (70.0)	6 (60.0)	8 (80.0)	–	69 (51.9)	28 (62.2)	26 (41.3)	15 (60.0)	440 (60.4)	157 (65.1)	109 (50.5)	174 (64.2)
	Alcohol consumption, *n* (%)	4 (20.0)	2 (20.0)	2 (20.0)	–	23 (17.3)	9 (20.0)	7 (11.1)	7 (28.0)–	150 (20.6)	52 (21.6)	25 (11.6)	73 (26.9)
	Tabaco consumption, *n* (%)	5 (25.0)	3 (30.0)	2 (20.0)	–	20 (15.0)	7 (15.6)	3 (4.8)	10 (40.0)	147 (20.2)	49 (20.3)	18 (8.3)	80 (29.5)
	BMI mean, (SD)	31.8 (5.0)	35.5 (3.1)	28.2 (3.6)	–	30.5 (4.2)	32.3 (2.4)	30.3 (4.8)	27.9 (3.5)	31.0 (4.6)	33.5 (2.9)	29.6 (4.4)	30.0 (5.0)
	HbA1c mean, (SD)	7.5 (1.0)	7.8 (0.8)	7.2 (1.1)	–	7.3 (1.1)	7.2 (1.0)	7.5 (1.2)	7.0 (1.1)	7.4 (1.3)	7.4 (1.1)	7.4 (1.3)	7.3 (1.3)
	HbA1c < 7%, *n* (%)	6 (30.0)	1 (10.0)	5 (50.0)	–	50 (37.6)	17 (37.8)	22 (34.9)	11 (44.0)	282 (38.7)	84 (34.9)	76 (35.2)	122 (45.0)
	HbA1c < 8%, *n* (%)	13 (65.0)	6 (60.0)	7 (70.0)	–	102 (76.7)	34 (75.6)	48 (76.2)	20 (80.0)	552 (75.8)	182 (75.5)	158 (73.1)	212 (78.2)
	Glomerular filtration mean, (SD)	72.2 (14.7)	76.1 (16.5)	68.4 (12.4)	–	70.7 (20.0)	73.8 (22.5)	69.0 (15.6)	69.6 (24.9)	77.6 (20.1)	77.4 (17.8)	68.0 (20.9)	85.3 (17.8)
	CAC mean, (SD)	16.5 (16.0)	12.8 (17.0)	20.2 (14.9)	–	58.7 (264.6)	23.7 (33.0)	94.9 (380.7)	30.7 (45.9)	60.7 (241.9)	58.7 (203.3)	78.7 (287.5)	48.2 (233.5)
	Number of visits with a physician mean, (SD)	3.4 (1.7)	3.7 (2.1)	3.0 (1.3)	–	4.5 (4.0)	5.9 (5.6)	3.7 (2.5)	4.0 (2.8)	3.8 (3.3)	4.0 (3.5)	4.4 (3.6)	3.2 (2.6)

BMI, body mass index; CPG, clinical practice guidelines; HbA1c, glycosylated hemoglobin; $^{+}$Moderate and high-risk alcohol consumption; SD, standard deviation.

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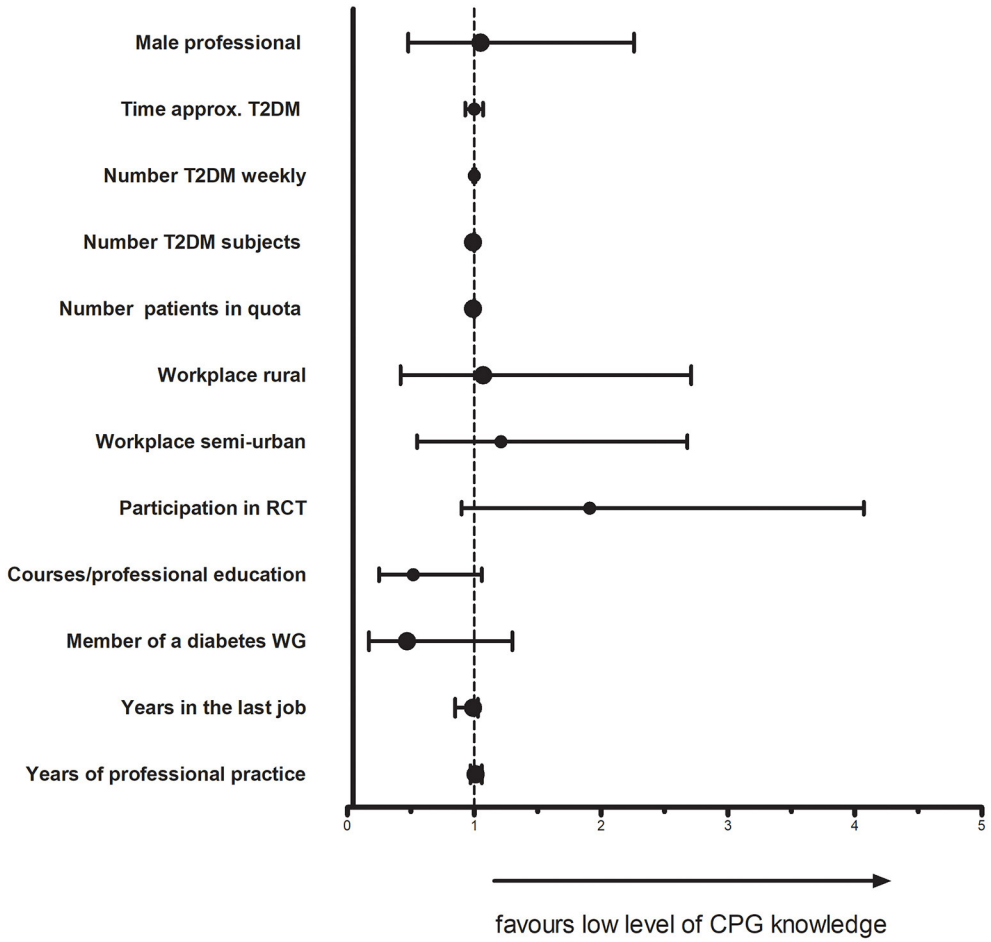

FIGURE 1
Factors related to the low level of CPG knowledge. CPG, clinical practice guidelines; RCT, randomized clinical tiral; T2DM, type 2 diabetes melitus; WG, working group.

especially in preventing possible complications or achieving correct therapeutic adherence.

We have to acknowledge some limitations in our study. Firstly, this was a cross-sectional observational study, where participants were selected due to their clinical profile, so inherent selection biases are possible. Secondly, the data collection was retrospective from the participant's medical records, so possible missing some variables possible, such as laboratory parameters or clinical variables related to physical examination, etc. On the other hand, the questionaries' used to evaluate a professional's degree of knowledge are not standardized or validated but just related to the recommendations available in current clinical guidelines. Moreover, those questionnaires were auto-administrated, so there is a possibility that person who was answering the questions could look for the answers in the clinical guidelines even though that time for answering was limited. Thirdly, additional inclusion criteria are just approximations for the definition of the three groups of T2DM patients, no specific test or functional probes were performed to identify/quantify the frailty (Barthel index or Lawton scale). Fourthly, the adherence to antidiabetic drugs was not evaluated in this study. Fifthly the professionals were not selected randomly but simply invited to participate in the study; therefore, there is a possibility of selection bias or that only highly motivated primary healthcare professionals took part in this study. Finally, the sample size in this paper is small, and the population is divided into three groups, which further weakens the statistical efficacy. The strengths of our study are the specific study design focused on professionals and patients, the number of participants, and the settings of realization. Primary care centers are the healthcare gate for participants with diabetes, they represent the clinical reality, and the results of this analysis have high external validity.

In conclusion, our cross-sectional analysis shows adequate adherence to the clinical guidelines by the primary care physicians for most participants with obesity, frailty, or newly diagnosed with T2DM. Specifically designed interventions are needed for professionals and participants with diabetes to improve the control and complications of type 2 diabetes in primary health care settings.

Data availability statement

The datasets presented in this article are not readily available due to the legal limitations, the dataset of this study is a property

of RedGDPS Foundation. Requests to access the datasets should be directed to JF-N, josep.franch@gmail.com.

Ethics statement

The study involves human participants, and it was reviewed and approved by IDIAP Jordi Gol Ethics Committee (protocol approval number 20/098-P, on 02/07/2020). The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization, methodology, and writing: BV and JF-N. Original draft preparation: BV. Review and editing: BV, MM-C, LR, JB-d, BF-C, and JF-N. Supervision and funding acquisition: JF-N. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

MM-C has received advisory and or speaking fees from Astra-Zeneca, Bayer, Boehringer Ingelheim, GSK, Lilly, MSD, Novartis, Novo Nordisk, and Sanofi; he has received research grants to the institution from Astra-Zeneca, GSK, Lilly, MSD, Novartis, Novo Nordisk, and Sanofi. JF-N has received advisory and or speaking fees from Astra-Zeneca, Ascensia, Boehringer Ingelheim, GSK, Lilly, MSD, Novartis, Novo Nordisk, and Sanofi; he has received research grants to the institution from Astra-Zeneca, GSK, Lilly, MSD, Novartis, Novo Nordisk, Sanofi, and Boehringer.

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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1138956/full#supplementary-material

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Using point-of-care HbA1c to facilitate the identification of diabetes and abnormal glucose regulation in primary healthcare settings

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Background: Glycated hemoglobin A1c (HbA1c) is a critical index for the diagnosis and glycemic control evaluation of diabetes. However, a standardized method for HbA1c measurement is unaffordable and unavailable among the Chinese population in low-resource rural settings. Point-of-care (POC) HbA1c testing is convenient and inexpensive, but its performance remains to be elucidated.

Objective: To investigate the value of POC HbA1c for identifying diabetes and abnormal glucose regulation (AGR) in the resource-limited Chinese population.

Methods: Participants were recruited from 6 Township Health Centers in Hunan Province. Samples for POC HbA1c, venous HbA1c, fasting plasma glucose, and 2 h-plasma glucose were obtained after physical examination. The oral glucose tolerance test was performed as the gold standard for diagnosis. The diagnostic capacities of the POC HbA1c measurement in predicting undiagnosed diabetes and AGR were evaluated.

Results: Among 388 participants, 274 (70.6%) normoglycemic controls, 63 (16.2%) prediabetes patients, and 51 (13.1%) diabetes patients were identified with oral glucose tolerance test (OGTT). Meanwhile, among 97 participants who underwent two HbA1c detection methods simultaneously, a positive correlation was found between POC HbA1c and standardized HbA1c ($r = 0.75$, $P < 0.001$). No notable systematic difference was observed from the Bland-Altman Plots. The POC HbA1c cutoff values were 5.95 and 5.25%, which efficiently identified diabetes (AUC 0.92) and AGR (AUC 0.89), respectively.

Conclusions: The alternative POC HbA1c test efficiently discriminated AGR and diabetes from normoglycemia, especially among the Chinese population in primary healthcare settings.

KEYWORDS

point-of-care, HbA1c, diabetes, abnormal glucose regulation, primary healthcare settings, China

Introduction

Diabetes has been a major public health crisis around the world, with more than half a billion people living with diabetes (1). The prevalence of diabetes is high and increasing in China. A national survey indicated that the prevalence of diabetes and prediabetes was 12.8 and 35.2%, respectively, among adults living in China. However, diabetes and prediabetes

remain undiagnosed in up to 50% of people with these disorders (1). Early identification of diabetes and prediabetes provides an opportunity to commence effective preventive treatment that leads to improved health outcomes (2–4). Therefore, early identification of diabetes through a reliable and convenient screening test is becoming a major health priority.

Although many scientific societies recommend screening for diabetes in the general population, there is currently no international consensus for screening strategies (5, 6). Three approaches are commonly used to detect diabetes and prediabetes: fasting plasma glucose (FPG), the oral glucose tolerance test (OGTT) and glycated hemoglobin A1c. These three methods have their own advantages and limitations. FPG has been proven to be feasible, convenient and reproducible but has low sensitivity and high preanalytical variability. While the OGTT is verified to be more sensitive, this approach is poorly accepted due to its poor reproducibility, cumbersome procedure and questionable cost-effectiveness (7). The HbA1c test has several advantages, including greater convenience, greater reproducibility and greater stability during illness or stress (7, 8). However, high cost and limited availability in certain regions of developing countries are barriers to using this method widely (9, 10).

Point-of-care (POC) HbA1c can provide rapid "on-site" results using handheld devices and blood samples obtained by fingerstick. The device requires little expertise and is easy to operate with no major procedural challenges. Some studies have proven that it can be used to facilitate the identification of prediabetes and diabetes, especially in resource-limited settings, at a relatively lower cost (11–13). To the best of our knowledge, no relevant studies have been conducted in China. The aim of this study is to quantify the performance of POC HbA1c in identifying undiagnosed diabetes and abnormal glucose regulation (AGR) in an asymptomatic, resource-limited Chinese population.

Methods

Local primary care providers conducted the study and collected data from January 1 to December 31, 2021, at 6 Township Health Centers in Pingjiang County, Hunan Province. Native residents at least 18 years of age without previously diagnosed diabetes or prediabetes were eligible for the study. Individuals with severe anemia or those who recently experienced massive blood loss were excluded from the study. Native residents without previously diagnosed diabetes or prediabetes who were due for diabetes screening were invited to take part. The cross-sectional study was conducted on a real-world basis according to available resources. All participants provided written informed consent, and the study was approved by the ethics committee of the Second Xiangya Hospital of Central South University.

The sample size required was determined, using the estimate prevalence of AGR detected by OGTT and HbA1c and a formula for a comparative studies. At a significance level of 95%, power of 80%, estimated occurrence of AGR in the general population being 30% and hypothesized difference in prevalence of AGR between the two tests at 17%, the minimum computed sample size was 238 and adjusted to 388.

Measurements

Clinical staff determined fasting status and performed physical examinations and laboratory tests. Participants underwent physical measurements of weight, height, waist circumference (WC), body mass index (BMI), and blood pressure (BP). Height and weight were measured using a wall-mounted stadiometer and calibrated scales with participants standing up with no shoes and lightly clothed. Height and weight were measured to the nearest 0.5 cm and 0.1 kg, respectively. BMI was calculated as weight in kilograms divided by the square of height in meters. Waist circumference (WC) was measured in the horizontal plane midway between the 12th rib and iliac crest using flexible tape. WC was recorded to the nearest 0.5 cm. Blood pressure measurements were taken using a calibrated electronic BP device (OMRON) with the participant seated. Before the measurement, the participants were asked to sit silently for 5–10 min.

The laboratory assessment included a capillary POC finger-prick HbA1c measurement, laboratory HbA1c, fasting plasma glucose levels (FPG) and two-hour plasma glucose levels (2-h PG) after carrying out an oral 75 g glucose tolerance test. For POC HbA1c measurement, one blood drop was obtained by fingerstick and placed on a separate applicator. Then, a trained nurse performed the HbA1c measurement with a portable HbA1c testing system (Sinocare, China, measurement range 4.0–15.0%). Whole blood samples were collected in EDTA tubes (HbA1c test) and fluoride/oxalate tubes (glucose test). Venous plasma glucose was measured by the glucose oxidase peroxidase method on an automatic biochemical analyzer (Mindray BS-180 Analyzer) at local Township Health Centers. Venous whole blood samples for HbA1c were stored at 4°C and sent to the laboratory of the Second Xiangya Hospital. HbA1c was measured by high-performance liquid chromatography (Bio-Rad VARIANT II Hemoglobin Analyzer), which is certified by the National Glycohemoglobin Standardization Program (NGSP).

OGTT was defined as the gold standard, and the ADA criteria were used to diagnose diabetes and prediabetes. Diabetes was diagnosed when FPG was $\geq$7.0 mmol/L or 2-h PG was $\geq$11.1 mmol/during OGTT. Prediabetes was diagnosed when FPG was 5.6 mmol/L to 6.9 mmol/L or 2-h PG during 75-g OGTT was 7.8 mmol/L to 11.0 mmol/L (6). AGR includes diabetes and prediabetes.

Statistical analysis

Data were analyzed with GraphPad Prism software version 8 (GraphPad Software, San Diego, CA) and SPSS version 25.0 (IBM Corporation, Chicago, IL). Data are presented as the mean $\pm$ SD, quartile or percentage of total. A normality test (Kolmogorov-Smirnov test) was performed before the data analysis. Comparisons between groups were made using One-Way Analysis test or nonparametric test. The agreement between venous plasma and POC HbA1c measurement was assessed with the Pearson correlation coefficient. Systematic differences between the HbA1c values obtained from venous plasma and POC HbA1c measurements were evaluated by Bland-Altman Plots

(14). Receiver operating characteristic curves (AUCs) were used to determine the ability of POC HbA1c to identify diabetes and AGR. $p < 0.05$ was considered statistically significant.

Results

A total of 388 participants were recruited, and POC HbA1c and OGTT were performed in all participants, whereas venous HbA1c was completed in 97 of all participants due to the inconvenience of specimen transportation. Of the 388 participants, 63 (16.2%) had undiagnosed prediabetes, and 51 (13.1%) had undiagnosed diabetes based on OGTT. Table 1 summarizes the characteristics of participants according to the different glucose tolerance categories.

Agreement between POC capillary and standard venous HbA1c measurement

POC capillary blood and venous HbA1c measurements showed a high positive correlation ($r = 0.75$, $P < 0.001$) (Figure 1A). No notable systematic difference was observed from the Bland and Altman Plots at any given blood HbA1c level, only 1 lower outlier and 3 upper outliers outside the agreement limits range (95% confidence intervals: −0.956 to 0.849) (Figure 1B).

Performance of POC HbA1c to identify diabetes and AGR

With the OGTT as the "gold standard" for detection of diabetes and AGR, POC HbA1c tests provided a highly discriminatory capacity for predicting the presence of diabetes with an AUC of 0.92. The most appropriate POC HbA1c threshold value for diagnosing diabetes was 5.95%. The sensitivity and specificity were 88.2 and 88.1%, respectively. The AUC for POC HbA1c tests in predicting AGR was 0.89. The most appropriate POC threshold value for diagnosing diabetes was 5.25% (Figure 2A; Table 2). The sensitivity and specificity were 89.5 and 77.4%, respectively (Figure 2B; Table 2). Meanwhile, the high NPV of POC HbA1c of 94.4% could rule out normal glucose tolerance individuals effectively (Table 2).

POC HbA1c is less costly and more convenient than the laboratory HbA1c method

The POC HbA1c test is less costly. Furthermore, it only requires one blood drop obtained by fingerstick and can provide rapid "on-site" results within several minutes. In contrast, the laboratory test requires a venous blood sample collected by a trained phlebotomist and 1–2 days to receive a definitive result (Table 3).

Discussion

Our study of the utility of POC capillary HbA1c in predicting undiagnosed diabetes and AGR in primary healthcare settings has three findings. First, there was a strong positive correlation between POC capillary HbA1c levels and venous laboratory HbA1c levels. Second, POC HbA1c demonstrated highly discriminatory capacity for identifying undiagnosed diabetes and AGR. Finally, the POC HbA1c test was less costly and more convenient than the venous laboratory HbA1c test.

Currently, the American Diabetes Association (ADA) recommends that diabetes and prediabetes be diagnosed by measuring the fasting plasma glucose (FPG) value or the 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT) or by A1C criteria (6). The HbA1c test has several advantages, including greater convenience, greater reproducibility and greater stability during illness or stress (7, 8). However, these advantages may be offset by the high cost and limited availability in certain regions of developing countries.

POC capillary HbA1c is a more attractive, alternative diagnostic test due to its lower cost and greater convenience. Typically, the POC HbA1c device uses a drop of blood obtained by fingerstick applied to a reagent cartridge, and the analysis is performed in a desktop analyzer. It can provide rapid "on-site" results within several minutes. Expert groups recommended using the POC HbA1c test to monitor glycemic control and guide outpatient decisions for patients with diabetes (6). This testing method can enable more timely treatment adjustments based on the immediate results. It is highly acceptable to physicians and patients. Clinical studies have demonstrated that it can significantly improve glycemic control compared to standard laboratory tests (15–17). However, the utility of POC HbA1c to diagnose diabetes or prediabetes is limited owing to concerns about the accuracy of this method, namely, its accuracy relative to a standard laboratory method (18). No large studies have been performed to evaluate the clinical performance of POC HbA1c testing compared with laboratory HbA1c testing. The reliability of POC HbA1c measurements has been debated since some studies have shown that some POC HbA1c devices may not be suitable for clinical use due to the high variation in accuracy (19, 20). However, some studies have been performed to evaluate the reliability of POC HbA1c devices, and the results showed that POC HbA1c devices, including the Siemens DCA Vantage™, A1C EZ 2.0 (Biohermes, Wuxi, China), etc., met the criteria for accuracy set by the National Glycohemoglobin Standardization Program (NGSP) (21, 22). A similar investigation was also performed in our study. The results showed that POC capillary blood and venous HbA1c measurements showed a high positive correlation ($r = 0.75$, $P < 0.001$). No notable systematic difference was observed from the Bland-Altman Plots at any given blood HbA1c level, with only 1 lower outlier and 3 upper outliers outside the agreement limit range. It is recommended that POC HbA1c should not be used to diagnose diabetes unless this method is validated as accurate (6, 23). We verified that POC HbA1c measurements in the present study showed a high level of agreement with laboratory testing and were an alternative method efficiently used to screen and diagnose diabetes or AGR in primary healthcare settings.

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TABLE 1 Characteristics of the entire study group and three glucose tolerance categories according to classification by oral glucose tolerance test results.

	All	NGT	Prediabetes	Diabetes	*p* value
No.	388	274	63	51	
Men (%)	215 (55.4%)	148 (54.0%)	40 (63.5%)	27 (55.4%)	0.367
Age (years)	63.0(55.0–70.0)	64.0 (54.0–70.0)	59.0 (55.0–67.0)	65.0 (59.0–70.0)	0.108
WC (cm)	80.0 (75.0–86.0)	78.0 (74.0–83.0)	84.0 (80.0–90.0)	91.0 (80.0–100.0)	<0.001
BMI (kg/m^2)	23.0 (21.4–24.9)	22.8 (21.3–24.1)	24.4 (21.9–26.4)	23.4 (21.5–27.2)	0.01
SBP (mmHg)	130.0 (124.0–138.0)	129.0 (123.0–136.0)	135.0 (123.0–141.0)	138.0 (128.0–150.0)	0.003
DBP (mmHg)	79.0(76.0–84.0)	78.0 (76.0–82.0)	80.0 (75.0–86.0)	85.0 (78.0–90.0)	<0.001
FPG (mmol/L)	5.0(4.7–5.4)	4.9 (4.7–5.2)	5.6 (4.6–6.0)	7.3(6.4–8.7)	<0.001
2-h PG (mmol/L)	6.8 (6.5–7.4)	6.7 (6.4–6.8)	8.0 (7.0–9.0)	12.5 (10.2–15.3)	<0.001
POC HbA1c (%)	5.2 (5.0–5.9)	5.0 (4.9–5.2)	5.7(5.4–6.2)	6.7 (6.2–7.6)	<0.001

Data are reported as the mean (SD), number (%). NGT, normal glucose tolerance; WC, wait circumference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; 2-h PG, two-hour plasma glucose level (2-hPG) after carrying out an oral 75 g glucose tolerance test.

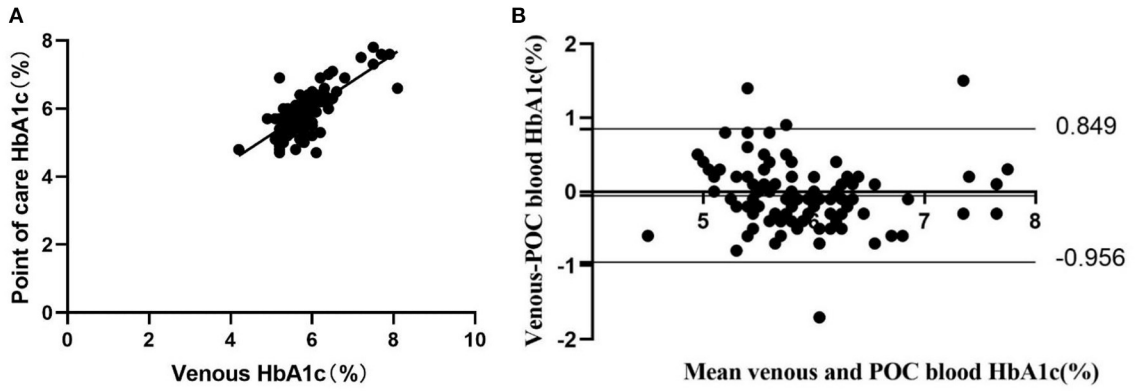

FIGURE 1
Concordance between laboratory venous blood HbA1c analysis and POC HbA1c analysis ($n = 97$). **(A)** Pearson correlation and scatter plot. **(B)** Difference vs. mean plot (Bland and Altman plot) of capillary blood HbA1c measured by POC and venous laboratory HbA1c measurement. The horizontal top and bottom lines represent ±2 SD.

TABLE 2 POC HbA1c cutoff points and utility with respect to diabetes and AGR.

	AUC	Cut point (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Diabetes	0.92	5.95	88.2	88.1	52.3	98.0
AGR	0.89	5.25	89.5	77.4	62.2	94.6

AGR, abnormal glucose regulation; AUC, area under curve; PPV, positive predictive value; NPV, negative predictive value.

Some clinicians have attempted to use POC HbA1c to screen or diagnose diabetes or prediabetes in certain settings or resource-limited regions (11–13). One study in the Australian indigenous population found that using a combination of POC and laboratory HbA1c could simplify diabetes screening in remote areas (11). Another study in a dental setting suggested that POC HbA1c could be a potential tool for abnormal glucose regulation (AGR) screening in a dental setting (12). Furthermore, a study conducted by a clinical pharmacist in America found that POC HbA1c facilitated the identification of prediabetes in a timely and feasible fashion (13). To the best of our knowledge, there is minimal evidence regarding the performance of POC HbA1c testing for screening or diagnosing diabetes or prediabetes in China. With an increasing incidence and prevalence of diabetes, standard laboratory HbA1c instruments are usually inaccessible and unaffordable in the Chinese primary care setting. Accurate and effective POC HbA1c devices are urgently needed. Our data suggest that performing POC HbA1c measurements and using a threshold

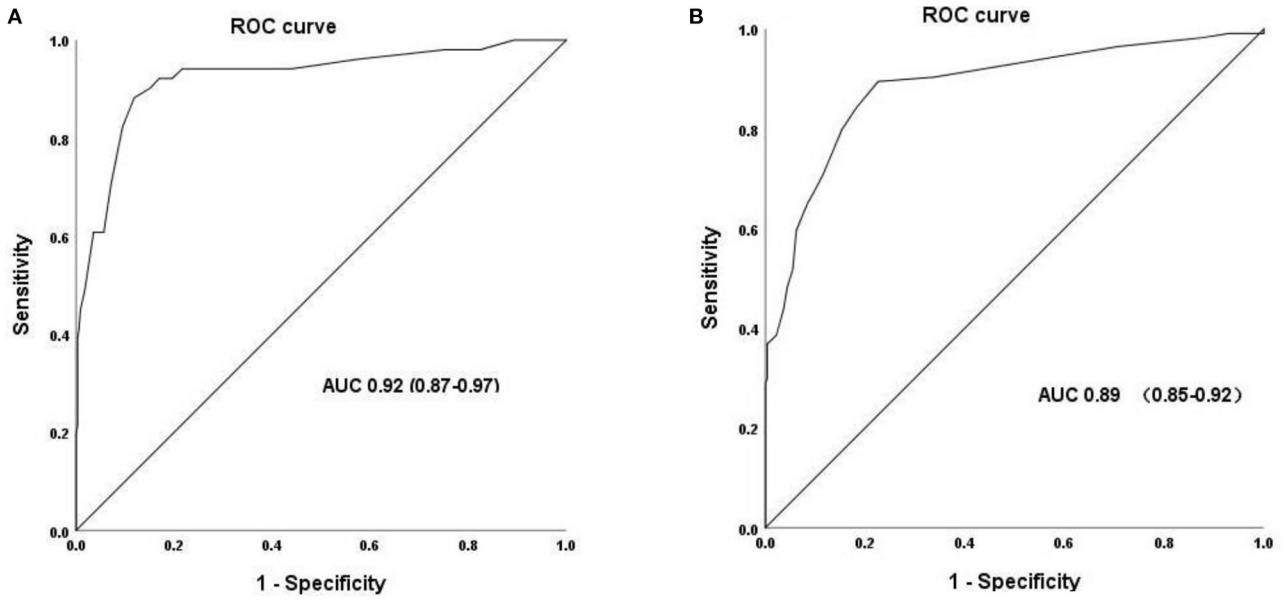

FIGURE 2
Receiver operating characteristic (ROC) curve for POC HbA1c to identify the presence of undiagnosed diabetes **(A)** and AGR **(B)**.

TABLE 3 The comparison between HbA1c measurement by POC and the standard laboratory method.

Item	POC HbA1c	Laboratory test of HbA1c
Unit Cost (yuan)*	15	45
Time to get the result	5 min	1–2 days
Required blood volume	One drop	2–3 ml
Blood collection method	Finger prick	Phlebotomy

*Unit cost in China.

of 5.95 or 5.25% can provide a high capacity for identifying diabetes (AUC 0.92) or AGR (0.89), respectively. In addition, POC HbA1c using the Sinocare device is less costly and more convenient than standard laboratory testing. This method may be a feasible and reliable method to identify diabetes or prediabetes and contribute to the prevention of diabetes in China, especially in remote, resource-limited rural region primary care settings.

There are several limitations in this study. First of all, this study was performed in one county in China, the results may not be generalized to other parts of China. Secondly, the number of participants were relatively small, further studies with larger participants are required to verify efficacy of POC HbA1c.

Conclusions

In conclusion, we verified a novel POC HbA1c device (Sinocare) in primary healthcare settings and found that its performance met the criteria for accuracy. In addition, our results support the use of the POC capillary HbA1c test for identifying diabetes or AGR in remote, resource-limited primary healthcare settings. Studies evaluating the cost-effectiveness of introducing POC HbA1c testing are needed prior to generalizing this method.

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 of the Second Xiangya Hospital of Central South University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

XS and ZW designed the study. LP collected the data, conducted the data analysis, and drafted the manuscript. XS, ZW, and ZZ revised the manuscript. YZ carefully edited the revised manuscript. All authors read and approved the submitted version of the manuscript.

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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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