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Association of metabolically healthy overweight/obesity with none of metabolic abnormalities with incident hyperglycemia in Chinese adults: a 5-year cohort study

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Abstract

Objectives: To explore whether metabolically healthy overweight (MHOW) and/or metabolically healthy obesity (MHO) increase hyperglycemia risk in a Chinese population with a board age range.

Design: Retrospective cohort study with health check from 2010 to 2016.

Setting and participants: A total of 47391 metabolically healthy participants with none of metabolic abnormalities were selected from 32 sites and 11 cities in China. Cox-proportional hazard model was employed to estimate the association of MHOW and MHO for incident hyperglycemia.

Primary and secondary outcome measures: hyperglycemia include incident diabetes and IFG. Diabetes was diagnosed with fasting blood glucose ≥7.0 mmol/L and/or on self-report during follow-up. The FPG level of IFG was from 5.6 to 6.9 mmol/L.

Results: With an average follow-up of 3.06 years, 5274 participants (11.13%) developed hyperglycemia over 144,804 person-years, with an incidence rate of 36.42 per 1000 persons-years. Adjusted model revealed a higher risk of incident hyperglycemia in the MHOW group (HR=1.23, 95%CIs: 1.16 to 1.30) and the MHO group (HR=1.49, 95% CI: 1.33 to 1.67) compared with the MHNW group. With 1 unit increase of BMI, the risk of hyperglycemia increased by 6% (HR = 1.06, 95% CI: 1.04 to 1.07). The stratified analyses and interaction tests showed the robustness of the association, and there were a stronger association in women (*P* for interaction <0.001).

Conclusions: The MHOW and MHO phenotypes were positively associated with higher risk of hyperglycemia in this population. And the association was particularly stronger in women. Early screening and weight management can help lower the hyperglycemia incidence in metabolically healthy population.

Strengths and limitations of this study

1. This retrospective cohort study was representative of Chinese population with a large sample size and a broad age range.
2. The metabolically healthy status was defined strictly based on NCEP ATP-III criteria with none of metabolic abnormalities.
3. The index of WC was not measured at baseline, we cannot predict the risk of hyperglycemia among abdominally obese individuals.
4. The other confounding factors, such as physical activity and dietary factors were not included in analysis.

Introduction

About 537 million adults across the world were diagnosed with diabetes mellitus, and over 90% was type 2 diabetes mellitus (T2DM)[1]. In addition, prediabetes has become an epidemic phenomenon. In 2021, 6.2% of the adult population in the world are impaired fasting glucose (IFG) or 10.6% are impaired glucose tolerance (IGT)[1]. Among Chinses adults, the prevalence of diabetes and prediabetes was high and increased from 2013 to 2018[2, 3], with the prevalence was about 12.4% and 38.1% in 2018[3].

Global obesity prevalence increased gradually since the early 1980s[4], which is one of the critical risk factors of diabetes mellitus. However, some obese individuals, who do not have other major cardiovascular risk factors, named metabolically healthy obesity (MHO). However, the MHO phenotype likely evolves towards metabolically unhealthy obesity, which may increase cardiovascular disease risk and mortality over time.

Importantly, the definition of MHO is inconsistent at present. The most common definition of MHO is based on the criteria provided by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III)[5], and most definitions require fewer than two of criteria factors except for waist circumference (WC)[6]. A systematic review reported that MHO prevalence was from 6% to 75%, and this may vary due to unified definition and social demographic[7]. In a Chinese adult population, the MHO prevalence varied between 13.6% when using the homeostasis model assessment criteria, 11.4% using the Chinese Diabetes Society criteria, and 10.3% using ATP-III criteria[8].

Compared with the metabolic healthy normal weight (MHNW) individuals, whether the risk of diabetes increase of MHO population is interesting. There were some studies indicated that MHO individuals were not at increased risk for diabetes compared with MHNW individuals[9, 10], however, other studies showed that MHO was associated with an increased risk of diabetes[11, 12]. Furtherly, the association was not significant with the MHO defined with none of metabolic abnormalities[11, 12]. In addition, the inconsistent results were correlated with the different age range of the population. The participants were middle-aged under 60 years in most of the previous studies[9, 10, 13-15], however, in China the studies mainly focused on the elderly individuals[11, 12, 16].

Therefore, we illustrated the association of hyperglycemia (including diabetes and IFG) among the young, middle-aged and elderly metabolically healthy individuals without any metabolic abnormalities of the ATP-III criteria from a large cohort Chinese population.

Methods

Subjects

Raw data were download from the "DATADRYAD" database (www.datadryad.org) provided by Chen et al. [17]. This secondary analysis did not violate the authors rights, as the authors waived the copyright[17].

The information of 211,833 individuals was introduced in detail by Chen et al. [17]. As this present study focus on metabolically healthy status, we further excluded participants with (1) BMI < 18.5 kg/m^2 (n=12081); (2) systolic blood pressure (SBP) ≥130 mmHg and/or diastolic blood pressure (DBP) ≥ 85 mmHg or no available blood pressure value (n=61440); (3) fasting plasma glucose (FPG) ≥ 5.6 mmol/L (n=1618); (4) triglyceride (TG) ≥ 1.7 mmol/L or no available TG (n=28504); (5) high density lipoprotein cholesterol (HDL-C) ≤ 1.04 mmol/L (men) or ≤ 1.29 mmol/L (women) or no available HLD-C (n=60799), and finally 47391 individuals were included. The flowchart is shown in Fig. 1.

Data collection

As described in the original study, the basic information was collected by questionnaire, and anthropometric data were measured in a standardized way. Blood pressure was measured by standard mercury sphygmomanometers. Fasting blood was collected to measure glucose levels, TG, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), HDL-C, aspartate transaminase (AST), and the alanine transaminase (ALT) by an autoanalyzer (Beckman 5800).

Definitions of obesity, metabolic health

Body weight was categorized based on BMI to normal weight (18.5-23.9 kg/m^2), overweight (24.0-27.9 kg/m^2), and obese (≥ 28.0 kg/m^2). WC was not used due to the collinearity with BMI[14]. Metabolically healthy status was defined based on NCEP ATP-III criteria[5] as the absence of any metabolic abnormalities, which include: (1) systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg; (2) TG ≥ 1.7 mmol/L; (3) FPG ≥ 5.6 mmol/L; (4) HDL-C ≤ 1.03 mmol/L in men or ≤ 1.29 mmol/L in women. According to BMI categories and metabolically healthy status, the participants were divided into three phenotypes: (1) MHNW, (2) MHOW, (3) MHO.

Outcome Measures

Hyperglycemia (dichotomous variable: 0 = non- Hyperglycemia, 1 = Hyperglycemia). In this study, hyperglycemia include incident diabetes and IFG. Diabetes was diagnosed with fasting blood glucose ≥7.0 mmol/L and/or on self-report during follow-up. The FPG level of IFG was from 5.6 to 6.9 mmol/l based on the American Diabetes Association criteria[18].

Covariates

The screening of covariates is based on previous literature[11, 12, 16, 17, 19, 20], which included: (1) continuous variables: age, ALT, AST, LDL-C, TC, blood urea nitrogen (BUN), and serum creatinine (SCr); (2) categorical variables: gender, smoking status, drinking status, and family history of diabetes.

Missing Data Processing

The missing data for LDL-C: 26 (0.17%), ALT: 35 (0.23%), AST: 8,120 (53.75%), BUN: 354 (2.34%), SCr: 113 (0.75%), drinking status: 10,473 (69.33%), and smoking status: 10,473 (69.33%), respectively. Multiple imputation was used for missing continuous variables in the present study. This module uses a chain algorithm and uses R's MI package for multiple interpolation. Treated as categorical variables for the missing data of categorical variables [21].

Statistical Analysis

Basic characteristics were presented as mean ± SD or percentage. One-way ANOVA or Kruskal-Wallis test for continuous variables and χ^2 test for categorical variables were analyzed for group comparisons.

Kaplan-Meier survival method and Cox-proportional hazard model were employed to estimate the association of MHOW and MHO for incident hyperglycemia. According to the STROBE statement recommendation[22], the crude, minor- and full adjustment models were presented. In addition, a restricted cubic spline (RCS) model was constructed to explore the dose-response relationship between BMI and hyperglycemia prevalence.

We performed subgroup analyses to verify the modification effects of age, gender and family history of diabetes on the correlation of BMI with hyperglycemia. And the interaction effects were conducted between BMI categories and the corresponding subgroup variable. Sensitivity analysis was performed by considering diabetes or IFG as outcome separately.

All data were analyzed with R software (version 4.3.3) and Empower Stats (version 4.1). A two-sided *P*-value < 0.05 was set as statistically significant.

Patient and public involvement

Patients were not involved in the design, or conduct, or reporting, or dissemination plans of our research, because this program was a retrospective study.

Results

Basic characteristics of the study participants

A total of 47391 metabolically healthy participants (47.66% male) were finally included. The mean age and BMI were 40.95± 11.05 years and 22.48±2.59 kg/m^2, respectively. During 3.06± 0.95 years follow-up period, 5274 participants (11.13%) developed hyperglycemia. The characteristics stratified by BMI categories and the status of blood glucose were presented in Table 1 and Supplementary Table 1. Participants with higher BMI generally had higher FPG, SBP, DBP, TG, TC, LDL-C, ALT, AST, BUN, SCr, lower HDL-C, and had a higher percentage of male, current smoker and current drinker (P < 0.001; Table 1). During follow-up, all of the characteristics of hyperglycemic participants were different with participants without hyperglycemia (P < 0.05; Supplementary Table 1).

The univariate analysis for hyperglycemia in the metabolically healthy population

Supplementary Table 2 showed that higher age, BMI, FPG, DBP, SBP, TG, TC, LDL, AST, ALT, current drinker and smoker, and lower HDL-C were the risk factors of hyperglycemia. The females have a lower risk than the males. In Fig. 2, the Kaplan-Meier curve showed higher hazards were determined among MHOW and MHO (log-rank test, P < 0.001).

The association of MHOW/MHO and hyperglycemia risk among metabolically healthy participants

In metabolically healthy participants, 5274 individuals developed hyperglycemia over 144,804 person-years of follow-up, and the overall rate of hyperglycemia was 36.42 per 1000 person-years. The rate of hyperglycemia was 29.35 in MHNW group, 54.07 in MHOW group, and 72.24 in MHO group per 1000 person-years, respectively.

The hazard ratio (HR) and 95% confidence intervals (CI) of the BMI categories on the incidence of hyperglycemia were listed in Table 2. In the crude model, compared with MHNW participants, the risk of hyperglycemia in MHOW group increased 85% (HR = 1.85, 95% CI:1.75 to 1.97), and the risk in MHO group increased 163% (HR = 2.63, 95% CI:2.35 to 2.95), respectively. After adjusted for age, gender, and the family history of diabetes, the HR (95% CI) in MHOW group and MHO group was 1.51 (1.42, 1.60) and 2.10 (1.88, 2.36). Furtherly, after adjusting all the covariates, the relationship still exists, as the HR (95% CI) was 1.23 (1.16-1.30) for MHOW and 1.49 (1.33-1.67) for MHO, *P* for trend <0.001. By taking BMI as a continuous variable, we furtherly analyzed the correlation between BMI and hyperglycemia risk. The risk of incident of hyperglycemia increased by 6% (HR = 1.06, 95% CI:1.04 to 1.07, P < 0.001) with 1 unit increase of BMI.

The RCS model showed the risk of hyperglycemia increased gradually with increasement of BMI, even the significant relationship was nonlinear (*P*< 0.001, *P*-nonlinearity = 0.039, Supplementary Fig.1).

Subgroup analyses and sensitivity analyses

The stratified analyses and interactions effects were performed and the results were summarized in Table 3. The additive interactions between MHOW/MHO and hyperglycemia risk were observed in gender, and stronger correlation was found in female participants. However, no significant interaction was found in age or family history of diabetes.

In addition, the sensitivity analyses of the risk of diabetes and IFG were furtherly performed to inspect the robustness of the results (Supplementary Table 3). After adjusted for the covariates, the HR (95% CI) of incident diabetes was 1.39 (1.05-1.85) for MHOW and 2.91 (1.94-4.37) for MHO, *P* for trend <0.001; the HR (95% CI) of IFG was 1.23 (1.16, 1.31) for MHOW and 1.49 (1.32,1.68) for MHO, *P* for trend <0.001.

Discussion

The association between the BMI categories and incident hyperglycemia in the metabolically healthy population was examined in this cohort study. Compared with the MHNW group, the risk of hyperglycemia gradually increased in the MHOW group and MHO group. And, an increasing trend of incidence of hyperglycemia with a higher BMI. This present study suggests that the presence of MHOW/MHO, even with the absence of metabolic risk factors, significantly increased the incidence of hyperglycemia. MHOW and/or MHO should not be treated as a healthy status, and weight management maybe an effective way for prevention of hyperglycemia and its related metabolic diseases among MHOW or MHO individuals.

The BioSHaRE-EU Healthy Obese Project have shown that the MHO prevalence of was 7%-28% for women, and 2%-19% for men [23]. The MHO prevalence ranged from 4.2% in a Chinese cohort[8] to 13.3% among Asian Indians[24] and 28.5% in African Americans[25]. In this study, the prevalence of MHOW (21.93%) and MHO (3.25%) were lower than previous reports, due to metabolically healthy status was strictly defined with none of metabolic abnormalities.

Wu et al. have shown the positive effect of MHO on diabetes based on large

numbers of epidemiological studies worldwide[6]. However, the correlation was weakened when metabolically healthy status was defined with none of metabolic abnormalities. Evidently, the incidence of diabetes increased by 35-67% with one metabolic abnormality addition among metabolic healthy participants[26]. For example, Feng et.al found that the risk of diabetes was increased in the MHO individual among 49,702 older people, but the association was not significantly when MHO was characterized with no ATP-III risk factors[11]. In addition, Wei et.al found the increased risk of diabetes for MHO, but the elevated incidence was not statistically significant among MHO individuals with none of metabolic abnormalities in Dongfeng Tongji cohort study[12].

However, we still found a higher risk of hyperglycemia in MHOW group and MHO group as metabolically healthy status defined without any metabolic abnormalities in our study. What's more, we found the positive association of MHOW/MHO phenotype on diabetes and IFG, respectively. In consistent, compared with MHNW young men, the risk of diabetes among those MHOW or MHO individuals with absence of metabolic abnormalities were 1.89 and 3.88 times[26]. The results were inconsistent may be related with the following reasons. Firstly, the difference of age may partly explain the inconsistent results. The age of the individuals was 63.2 years[11] and 66 (63-71) years[12], while the mean age in our study was 40.95± 11.05 years. The young MHO adults conferred a higher hyperglycemia risk, because they are more likely to develop different metabolic abnormalities in the short term, while the middle-aged MHO population who were likely overweight or obese for years without developing diabetes or metabolic disorders. In addition, as is known, the "metabolically health" status without metabolic abnormalities becomes less with aging[23], so the numbers of MHOW and MHO in the former studies[11, 12] were obviously less than this present study.

Notably, interaction between gender and BMI categories on incident hyperglycemia was significant, as the risk of women was higher than men. This result was in line with some[27, 28], but not all previous studies[29, 30]. A cohort study found that the diabetes risk and IFG in obese women was higher[27]. Similarly, the other prospective case-cohort study observed that, particularly in women, WC was strongly associated with T2DM [28]. However, the greater HRs of diabetes in men with per SD increasement of BMI than in women (P for heterogeneity < 0.001) was found based on China Kadoorie Biobank study[30]. The previous studies have shown that obesity as the risk factor of diabetes was more common and stronger in women[31, 32].

The mechanism of positive association between BMI and hyperglycemia incidence in metabolic healthy population still remains unclear. However, to some content, the correlation may be interpreted by the increased inflammation and insulin resistance of MWOW and/or MHO phenotypes. As we all know, overweight and/or obesity have been always chronic low-grade inflammatory status, especially in insulin sensitive tissues, like liver, muscle and adipose tissues[33]. There was evidence showed that, even in MHO subjects, chronic inflammation plays critical role in diabetes development[34, 35]. Adipose tissue pro-inflammatory macrophages accumulation and infiltration was the most important cause of chronic inflammation[36]. Pro-inflammatory cytokines

mainly secreted from macrophages, such as tumor necrosis factor (TNF-α) and interleukin-1 beta (IL-1β), can trigger various signal pathway to induce insulin resistance. Critical signal pathways include TNF-α/ IKKβ/NF-κB, and TLR4/ NLRP3/caspase-1/IL-1β, which impair insulin action and modulate pancreas β-cell mass and function[37].

Study strengths and limitations

Apart from a large sample size and a broad age range, this study has several strengths. The metabolically healthy individuals were included without any metabolic risk factors, as to reveal the independent role of BMI and hyperglycemia risk. Furtherly, sensitivity analyses, subgroup analyses and interaction effects were examined to attest the reliability and stability of the results. There are several limitations of our study. Firstly, the index of WC was not measured at baseline, we cannot combine WC and BMI to distinguish people with abdominally obesity and cannot predict the risk of hyperglycemia among abdominally obese individuals. In addition, the hyperglycemia prevalence may be underestimated as the random plasma glucose and/or postprandial plasma glucose level were not collected. Finally, although numerous confounding factors were included, some potential factors may exist, such as physical activity and dietary factors.

To conclude, this study demonstrated that MHOW and MHO were independently positively associated with risk of incident hyperglycemia in absolutely metabolically healthy adults, and the correlation was particularly stronger in women. Considering the unsteady characteristics of metabolically healthy/obese phenotypes, these findings stress that early screening and weight control was necessary to lower hyperglycemia risk and to promote population health.

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Footnotes

Contributions

QG, QTY and SLJ: study design. QG, BYL and HML: data cleaning and analysis. QG, BYL, HML and RNX: result interpretation. QG, BYL, HML and RNX: manuscript writing. BYL and HML: manuscript editing. All authors approved the final manuscript.

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Data availability statement

Data sharing statement Extra data can be accessed via the Dryad data repository at

http://datadryad.org/withthedoi:10.5061/dryad.ft8750v.

Ethics statements

Patient consent: Not required.

Ethics approval: This study was approved by the Rich Healthcare Group Review Board, and the information was retrieved retrospectively.

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Table 1 The characteristics of the study participants stratified by BMI group.

Variables	Total	MHNW	MHOW	MHO	*P*-value
N	47391	34920	10932	1539	
Age (years)	40.95 ± 11.05	40.10 ± 10.70	43.38 ± 11.60	42.93 ± 12.07	<0.001
Male, n (%)	22586 (47.66)	14124 (40.45)	7369 (67.41)	1093 (71.02)	<0.001
BMI (kg/m^2)	22.48 ± 2.59	21.25 ± 1.48	25.41 ± 1.05	29.56 ± 1.69	<0.001
FPG (mmol/L)	4.82 ± 0.52	4.78 ± 0.52	4.92 ± 0.52	4.99 ± 0.54	<0.001
SBP (mmHg)	110.88 ± 10.24	109.65 ± 10.30	114.07 ± 9.31	116.26 ± 8.63	<0.001
DBP (mmHg)	69.23 ± 7.47	68.45 ± 7.43	71.22 ± 7.14	72.63 ± 7.13	<0.001
TG (mmol/L)	0.92 ± 0.34	0.87 ± 0.32	1.06 ± 0.33	1.16 ± 0.32	<0.001
TC (mmol/L)	4.69 ± 0.80	4.65 ± 0.80	4.79 ± 0.80	4.84 ± 0.79	<0.001
HDL-C (mmol/L)	1.50 ± 0.26	1.53 ± 0.27	1.42 ± 0.23	1.38 ± 0.21	<0.001
LDL-C (mmol/L)	2.70 ± 0.62	2.66 ± 0.61	2.80 ± 0.62	2.85 ± 0.63	<0.001
ALT (mmol/L)	22.49 ± 10.50	21.66 ± 10.15	24.46 ± 10.94	27.46 ± 11.82	<0.001
AST (mmol/L)	20.22 ± 18.34	18.05 ± 16.65	25.39 ± 20.72	32.80 ± 23.65	<0.001
BUN (mmol/L)	4.63 ± 1.16	4.56 ± 1.14	4.84 ± 1.17	4.91 ± 1.13	<0.001
SCr (mmol/L)	68.87 ± 15.47	67.05 ± 14.79	73.92 ± 16.32	74.36 ± 14.91	<0.001
Smoking status, n (%)					<0.001
Current smoker	2049 (4.32)	1277 (3.66)	667 (6.10)	105 (6.82)	
Ever smoker	493 (1.04)	284 (0.81)	181 (1.66)	28 (1.82)	
Never smoker	10221 (21.57)	7600 (21.76)	2313 (21.16)	308 (20.01)	
Drinking status, n (%)					<0.001
Current drinker	249 (0.53)	144 (0.41)	85 (0.78)	20 (1.30)	
Ever drinker	2117 (4.47)	1274 (3.65)	740 (6.77)	103 (6.69)	
Never drinker	10397 (21.94)	7743 (22.17)	2336 (21.37)	318 (20.66)	
Family history of diabetes, n (%)					0.874
Yes	1061 (2.24)	789 (2.26)	239 (2.19)	33 (2.14)	

Table 2 Relationship between BMI categories and the risk of hyperglycemia among the metabolically healthy participants

	Case/N	Crude Model (HR, 95% CI)	Model I (HR, 95% CI)	Model II (HR, 95% CI)
Hyperglycemia				
BMI	5274/47391	1.14 (1.13, 1.15)	1.10 (1.09, 1.11)	1.06 (1.04, 1.07)
MHNW	3139/34920	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
MHOW	1798/10932	1.85 (1.75, 1.97)	1.51 (1.42, 1.60)	1.23 (1.16, 1.30)
MHO	337/1539	2.63 (2.35, 2.95)	2.10 (1.88, 2.36)	1.49 (1.33, 1.67)
P for trend		<0.001	<0.001	<0.001

Model I: we adjusted age, gender and the family history of diabetes;
Model II: we further adjusted baseline FPG, ALT, AST, BUN, SCr, smoking status and drinking status.

Table 3 Multivariate-adjusted HR (95% CI) of hyperglycemia among BMI categories in stratified analyses

	MHNW	MHOW	MHO	*P* interaction
Gender				<0.001
Male	1.00 (Ref.)	1.11 (1.03, 1.20)	1.32 (1.15, 1.51)	
Female	1.00 (Ref.)	1.43 (1.29, 1.58)	1.88 (1.52, 2.32)	
Age (years)				0.534
< 40	1.00 (Ref.)	1.32 (1.17, 1.48)	1.51 (1.21, 1.89)	
≥ 40	1.00 (Ref.)	1.22 (1.13, 1.31)	1.53 (1.34, 1.75)	
Family history of diabetes				0.290
yes	1.00 (Ref.)	1.23 (1.15, 1.30)	1.46 (1.30, 1.65)	
no	1.00 (Ref.)	1.05 (0.71, 1.55)	2.12 (1.07, 4.19)	

Adjusted for maternal gender (except gender subgroup), age (except age subgroup), family history of diabetes (except "family history of diabetes" subgroup), and baseline FPG, ALT, AST, BUN, SCr, smoking status and drinking status.

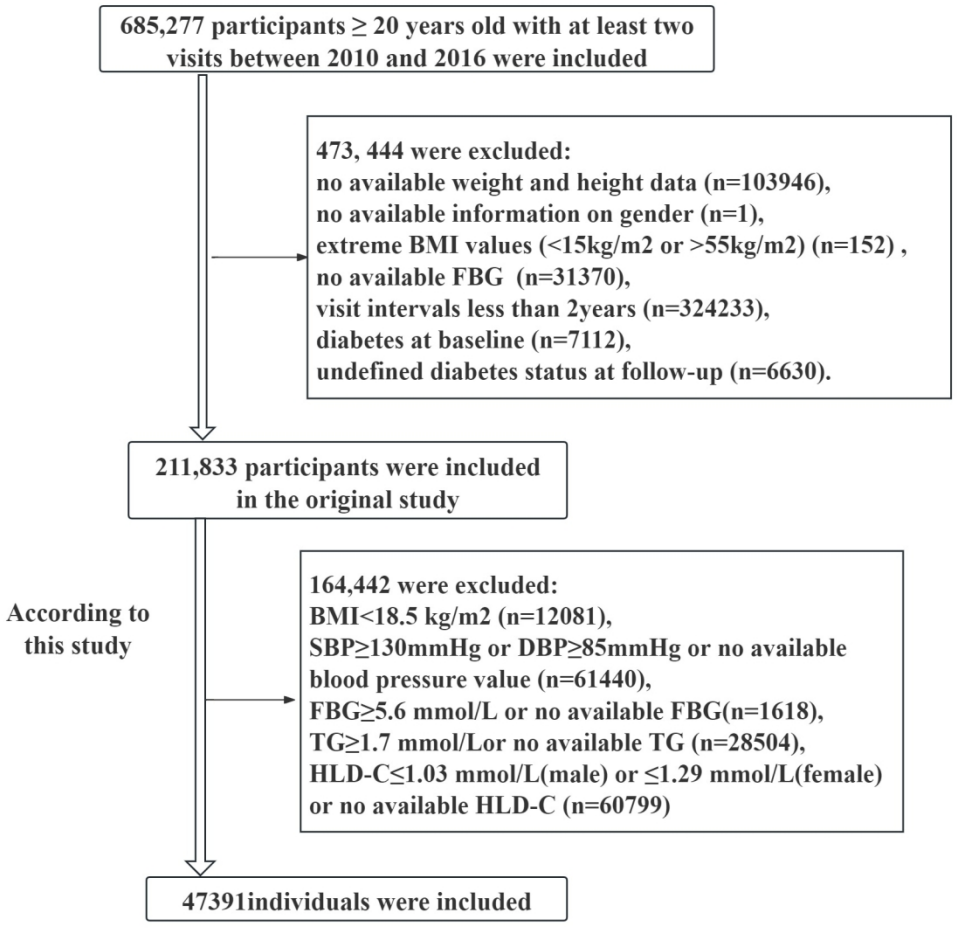


Figure 1. Study flow chart

Fig.1 Flowchart of this study.

630x666mm (72 x 72 DPI)

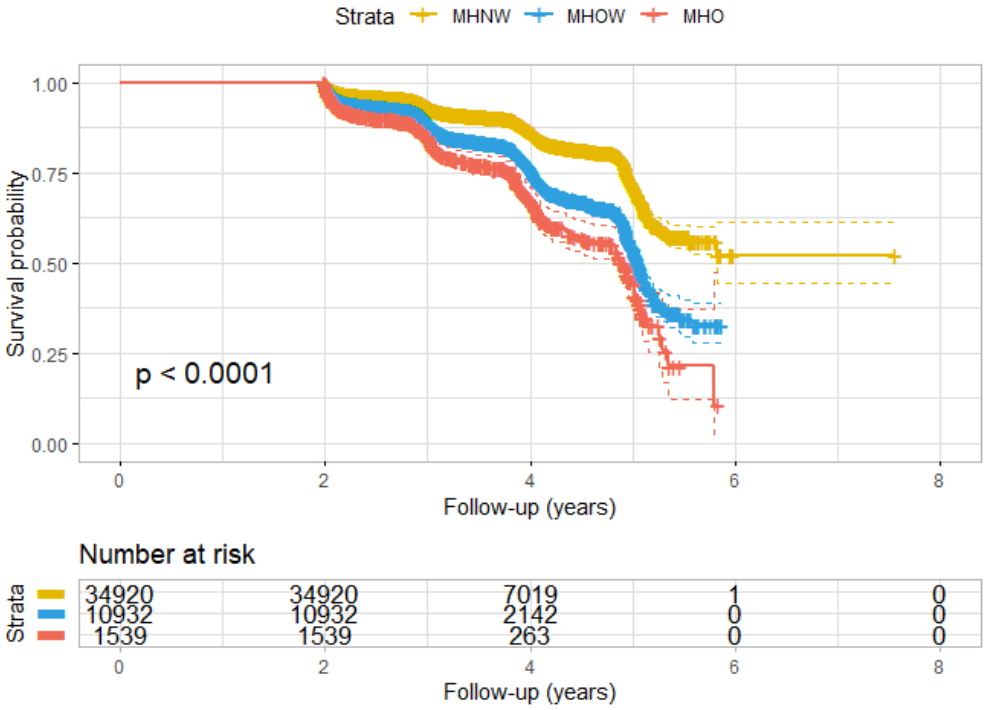


Fig.2 Kaplan-Meier curves for cumulative hazards of hyperglycemia incident risk. Figure showed that the cumulative risk of incident hyperglycemia was markedly different among the BMI categories (log-rank test, P< 0.001) and increased gradually with increase of BMI, resulting in maximum risk of prediabetes in the MHO group.

173x128mm (96 x 96 DPI)

Supplementary Table 1

The characteristics of the study participants with/without hyperglycemia

Variables	Non-hyperglycemia	Hyperglycemia	*P*-value
N	42117	5274	
Age (years)	40.25 ± 10.66	46.54 ± 12.48	<0.001
Male, n (%)	19401 (46.06)	3185 (60.39)	<0.001
BMI (kg/m^2)	22.35 ± 2.53	23.48 ± 2.81	<0.001
FPG (mmol/L)	4.77 ± 0.51	5.20 ± 0.51	<0.001
SBP (mmHg)	110.53 ± 10.26	113.72 ± 9.70	<0.001
DBP (mmHg)	69.01 ± 7.48	70.95 ± 7.21	<0.001
TG (mmol/L)	0.91 ± 0.33	1.01 ± 0.34	<0.001
TC (mmol/L)	4.67 ± 0.80	4.83 ± 0.83	<0.001
HDL-C (mmol/L)	1.51 ± 0.26	1.46 ± 0.25	<0.001
LDL-C (mmol/L)	2.69 ± 0.62	2.79 ± 0.63	<0.001
ALT (mmol/L)	22.35 ± 10.46	23.63 ± 10.71	<0.001
AST (mmol/L)	19.89 ± 18.03	22.92 ± 20.38	<0.001
BUN (mmol/L)	4.60 ± 1.15	4.88 ± 1.18	<0.001
SCr (mmol/L)	68.44 ± 15.46	72.27 ± 15.09	<0.001
Smoking status, n (%)			<0.001
Current smoker	1741 (4.13)	308 (5.84)	
Ever smoker	441 (1.05)	52 (0.99)	
Never smoker	9171 (21.78)	1050 (19.91)	
Drinking status, n (%)			0.003
Current drinker	211 (0.50)	38 (0.72)	
Ever drinker	1844 (4.38)	273 (5.18)	
Never drinker	9298 (22.08)	1099 (20.84)	
Family history of diabetes, n (%)			0.039
Yes	922 (2.19)	139 (2.64)	

Supplementary Table 2
The results of univariate analysis for the risk factors of hyperglycemia

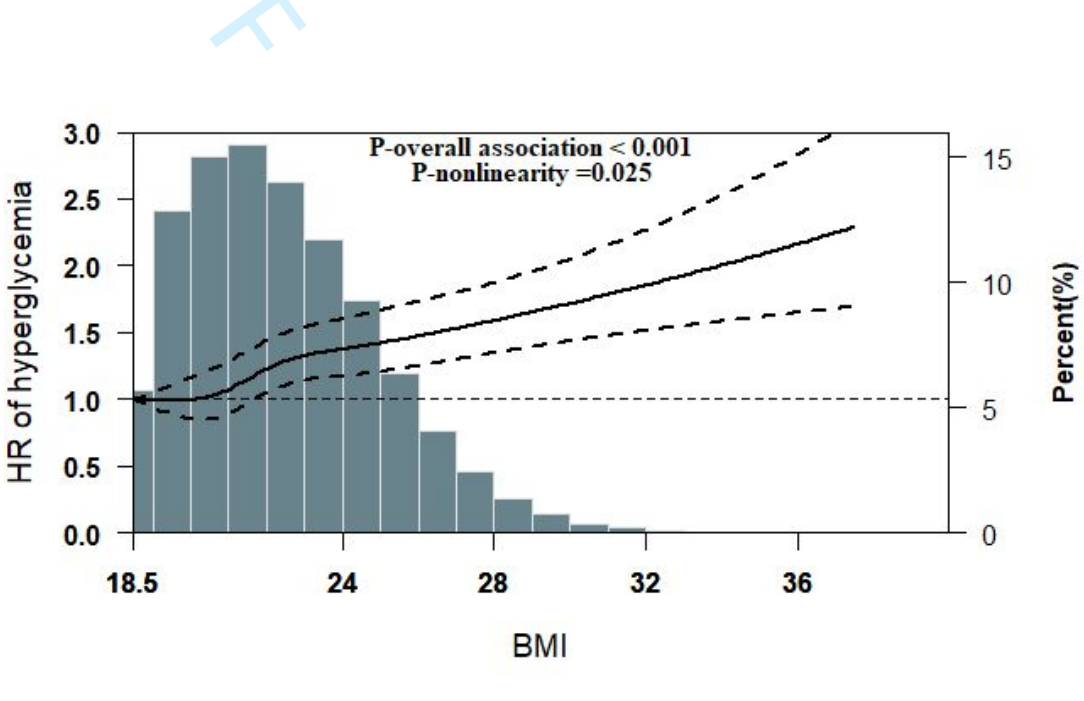
Covariables	HR (95%CI)	*P*-value
Age (years)	1.04 (1.03, 1.04)	<0.001
Gender		<0.001
Male	Ref.	
Female	0.60 (0.57, 0.64)	
FPG (mmol/L)	5.95 (5.63, 6.28)	<0.001
SBP (mmHg)	1.03 (1.03, 1.03)	<0.001
DBP (mmHg)	1.03 (1.02, 1.03)	<0.001
TG (mmol/L)	2.34 (2.17, 2.53)	<0.001
TC (mmol/L)	1.17 (1.13, 1.20)	<0.001
HDL-C (mmol/L)	0.62 (0.55, 0.68)	<0.001
LDL-C (mmol/L)	1.31 (1.26, 1.37)	<0.001
ALT (mmol/L)	1.00 (1.00, 1.00)	<0.001
AST (mmol/L)	1.01 (1.00, 1.01)	<0.001
BUN (mmol/L)	1.16 (1.14, 1.18)	<0.001
SCr (mmol/L)	1.01 (1.00, 1.01)	<0.001
Smoking status, n (%)		<0.001
Never smoker	Ref.	
Ever smoker	0.93 (0.70, 1.23)	
Current smoker	1.40 (1.23, 1.59)	
Drinking status, n (%)		<0.001
Never drinker	Ref.	
Ever drinker	1.15 (1.01, 1.31)	
Current drinker	1.56 (1.13, 2.15)	
Family history of diabetes		0.500
No	Ref.	
Yes	1.06 (0.90, 1.26)	

Supplementary Table 3

Relationship between BMI categories and the risk of diabetes/IFG among the metabolically healthy participants

	Case/N	Crude Model (HR, 95% CI)	Model I (HR, 95% CI)	Model II (HR, 95% CI)
Diabetes				
BMI	239/47391	1.24 (1.20, 1.28)	1.19 (1.14, 1.24)	1.14 (1.09, 1.18)
MHNW	116/34920	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
MHOW	91/10932	2.53 (1.92, 3.32)	1.78 (1.348, 2.36)	1.39 (1.05, 1.85)
MHO	32/1539	6.84 (4.62, 10.11)	4.55 (3.05, 6.78)	2.91 (1.94, 4.37)
P for trend		<0.001	<0.001	<0.001
IFG				
BMI	5035/47152	1.14 (1.13, 1.15)	1.10 (1.09, 1.11)	1.05 (1.04, 1.07)
MHNW	3023/34804	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
MHOW	1707/10841	1.85 (1.74, 1.96)	1.51 (1.42, 1.61)	1.23 (1.16, 1.31)
MHO	305/1507	2.54 (2.26, 2.86)	2.07 (1.83, 2.33)	1.49 (1.32,1.68)
P for trend		<0.001	<0.001	<0.001

Model I: we adjusted age, gender and the family history of diabetes;
Model II: we further adjusted baseline FPG, ALT, AST, BUN, SCr, smoking status and drinking status.



Supplementary Fig.1 Restricted cubic spline analyses illustrating the dose-response relationship between BMI and the incidence of hyperglycemia.

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Metabolically healthy overweight/obesity with no metabolic abnormalities and incident hyperglycemia in Chinese adults: analysis of a retrospective cohort study

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Metabolically healthy overweight/obesity with no metabolic abnormalities and incident hyperglycemia in Chinese adults: analysis of a retrospective cohort study

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Abstract

Objectives: To explore whether metabolically healthy overweight (MHOW) and/or metabolically healthy obesity (MHO) increase hyperglycemia risk in a Chinese population with a board age range.

Design: Retrospective cohort study.

Setting: Secondary analysis of data from the DATADRYAD database, comprising health check records of participants from 32 regions and 11 cities in China between 2010 and 2016.

Participants: A total of 47391 metabolically healthy participants with none of metabolic abnormalities were selected.

Primary and secondary outcome measures: hyperglycemia include incident diabetes and IFG. Diabetes was diagnosed with fasting blood glucose ≥7.0 mmol/L and typical clinical symptoms and/or on self-report during follow-up. The FPG level of IFG was from 5.6 to 6.9 mmol/L.

Results: With an average follow-up of 3.06 years, 5274 participants (11.13%) developed hyperglycemia over 144,804 person-years, with an incidence rate of 36.42 per 1000 persons-years. Adjusted model revealed a higher risk of incident hyperglycemia in the MHOW group (HR=1.23, 95%CIs: 1.16 to 1.30) and the MHO group (HR=1.49, 95% CI: 1.33 to 1.67) compared with the metabolic healthy normal weight group. With 1 unit increase of BMI, the risk of hyperglycemia increased by 6% (HR = 1.06, 95% CI: 1.04 to 1.07). The stratified analyses and interaction tests showed the robustness of the association, and there were a stronger association in women (*P* for interaction <0.001).

Conclusions: The MHOW and MHO phenotypes were positively associated with higher risk of hyperglycemia in this population. And the association was particularly stronger in women.

Strengths and limitations of this study

1. This retrospective cohort study is representative of the Chinese population, featuring a large sample size and a broad age range.
2. Metabolically healthy status was rigorously defined based on the NCEP ATP-III criteria with none of metabolic abnormalities.
3. Waist circumference was not measured at baseline, limiting the ability to assess the risk of hyperglycemia in individuals with abdominal obesity.
4. Other confounding factors, such as physical activity and dietary factors, were not included in the analysis.

Introduction

Approximately 537 million adults worldwide have been diagnosed with diabetes mellitus, with over 90% being type 2 diabetes mellitus [1]. In addition, prediabetes has emerged as a global epidemic. In 2021, 6.2% of the adult population had impaired fasting glucose (IFG), and 10.6% had impaired glucose tolerance [1]. Among Chinese adults, the prevalence of diabetes and prediabetes remained high and increased between 2013 and 2018 [2,3], with an estimated prevalence of 12.4% for diabetes and 38.1% for prediabetes in 2018 [3].

The global prevalence of obesity has been steadily rising since the early 1980s [4], which is one of the key risk factors for diabetes mellitus. However, some obese individuals, classified as having metabolically healthy obesity (MHO), do not present with major cardiovascular risk factors. Nonetheless, the MHO phenotype may progress to metabolically unhealthy obesity over time, increasing the risk of cardiovascular disease and mortality.

A critical issue is the inconsistency in defining MHO. The most common definition of MHO is fewer than two of criteria factors of the metabolic syndrome or fewer than one abnormal factor excluding waist circumference (WC) [5,6]. In 2021, Zembic A et.al have proposed a new definition of MHO based on systolic blood pressure, waist-to-hip ratio and diabetes, and found the cardiovascular mortality risk of the MHO group was not increased when compared the metabolic healthy normal weight (MHNW) individuals [7]. A systematic review reported that the estimated MHO prevalence was about 50% using ≤ 2 metabolic syndrome factors, or 24% using low HOMA-IR, or 13% when defined with no metabolic abnormality [8]. The relationship between MHO and the risk of diabetes remains a topic of interest. Some studies have suggested that MHO individuals are not at increased risk for diabetes compared to their MHNW counterparts [9, 10], while others have shown that MHO is indeed associated with a higher risk of diabetes [11, 12]. Moreover, when MHO is defined strictly with no metabolic abnormalities, the association with diabetes risk appears less significant [11, 12]. Recent studies have shown that the multi-organ insulin sensitivity in MHO group was lower than the metabolically healthy and lean group [13]. These inconsistent findings may be partly due to the differing age ranges studied, as most previous research focused on middle-aged individuals under 60 years [9, 10, 14-16], whereas studies in China predominantly examined older populations [11, 12, 17].

Therefore, we aimed to investigate the association between hyperglycemia (including diabetes and IFG) and metabolically healthy individuals without any metabolic abnormalities, based on ATP-III criteria, across young, middle-aged, and elderly groups in a large cohort of the Chinese population.

Methods

Study design and subjects

This study was conducted by the Rich Healthcare Group across 32 sites and 11 cities in China. The subjects who received a health check from 2010 to 2016 were recruited, and the demographic, lifestyle, medical history and family history of chronic disease were collected by questionnaire investigation. As a retrospective cohort study, 685277 participants were selected with at least two visits. After excluding the participant who

meet the exclusion criteria, a total of 211833 participants (116123 male and 95710 female) were included (in Figure 1). The information of 211,833 individuals was introduced in detail, and the data were download from the "DATADRYAD" database (www.datadryad.org) by Chen et al. [18].

For this study, focusing on metabolically healthy status, we excluded participants with body mass index (BMI) < 18.5 kg/m² (n = 12,081); systolic blood pressure (SBP) ≥ 130 mmHg and/or diastolic blood pressure (DBP) ≥ 85 mmHg, or missing blood pressure values (n = 61,440); fasting plasma glucose (FPG) ≥ 5.6 mmol/L (n = 1,618); triglycerides (TG) ≥ 1.7 mmol/L or missing TG values (n = 28,504); or high-density lipoprotein cholesterol (HDL-C) ≤ 1.04 mmol/L (men) or ≤ 1.29 mmol/L (women) or missing HDL-C values (n = 60,799). A total of 47,391 individuals were included. The flowchart is shown in Figure 1.

Data collection

As described in the original study, basic information was collected via questionnaire, and anthropometric data were measured in a standardized manner. Blood pressure was measured using standard mercury sphygmomanometers. Fasting blood samples were collected to measure glucose, TG, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), HDL-C, aspartate transaminase (AST), and alanine transaminase (ALT) using an autoanalyzer (Beckman 5800).

Definitions of obesity, metabolic health

Body weight was categorized by BMI as follows: normal weight (18.5–23.9 kg/m²), overweight (24.0–27.9 kg/m²), and obese (≥ 28.0 kg/m²). WC was not used due to collinearity with BMI [15]. Metabolic health was defined according to the NCEP ATP-III criteria [5] as the absence of any metabolic abnormalities, which included: SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg; TG ≥ 1.7 mmol/L; FPG ≥ 5.6 mmol/L; and HDL-C ≤ 1.03 mmol/L in men or ≤ 1.29 mmol/L in women.

Based on BMI and metabolic health status, participants were classified into three phenotypes: (1) MHNW, (2) metabolically healthy overweight (MHOW), and (3) MHO.

Outcome Measures

The primary of outcome was hyperglycemia, defined as a dichotomous variable (0 = non-hyperglycemia, 1 = hyperglycemia). In this study, hyperglycemia include incident diabetes and IFG. Diabetes was diagnosed with fasting blood glucose ≥7.0 mmol/L and typical clinical symptoms and/or self-report diabetes mellitus during follow-up. The FPG level of IFG was from 5.6 to 6.9 mmol/l based on the American Diabetes Association criteria [19].

Covariates

Covariates were selected based on previous literature[11, 12, 17, 18, 20, 21], and included continuous variables (age, ALT, AST, LDL-C, TC, blood urea nitrogen [BUN], and serum creatinine [SCr]) and categorical variables (gender, smoking status, drinking status, and family history of diabetes).

Missing Data Processing

Missing data were as follows: LDL-C: 26 (0.05%), ALT: 35 (0.07%), AST: 27433 (57.89%), BUN: 354 (0.75%), SCr: 113 (0.24%), drinking status: 34628 (73.07%),

and smoking status: 34628 (73.07%), respectively. Multiple imputation was applied for missing continuous variables using a chained equation algorithm with the R's MI package. Missing categorical variables were treated as categorical in the analysis [22].

Statistical Analysis

Basic characteristics were presented as mean ± SD or percentage. Group comparisons were conducted using one-way ANOVA or the Kruskal–Wallis test for continuous variables, and the χ^2 test for categorical variables. The Kaplan-Meier survival method and Cox-proportional hazard model were used to estimate the association of MHOW and MHO for incident hyperglycemia. According to the STROBE statement recommendation [23], the crude, minor- and full adjustment models were presented. In addition, a restricted cubic spline model was also constructed to assess the dose-response relationship between BMI and hyperglycemia risk.

Subgroup analyses were performed to assess the modifying effects of age, gender, height, and family history of diabetes on the association between BMI and hyperglycemia. Interaction tests were conducted between BMI categories and these subgroup variables. Sensitivity analyses were carried out to assess the robustness of the findings: 1) we did similar analysis after considering diabetes and IFG as separate outcomes; 2) we excluded the participants with missing smoking and drinking status; 3) we excluded the participants with missing AST.

All analyses were conducted using R software (version 4.3.3) and Empower Stats (version 4.1). A two-sided P-value < 0.05 was considered statistically significant.

Patient and public involvement

None.

Results

Basic characteristics of the study participants

A total of 47391 metabolically healthy participants (47.66% male) were finally included. The mean age and BMI were 40.95± 11.05 years and 22.48±2.59 kg/m^2, respectively. During a follow-up period of 3.06 ± 0.95 years, 5,274 participants (11.13%) developed hyperglycemia. The characteristics stratified by BMI categories and the status of blood glucose are presented in Table 1 and Table S1. Participants with higher BMI generally had higher FPG, SBP, DBP, TG, TC, LDL-C, ALT, AST, BUN, and SCr levels, lower HDL-C level, and had a higher proportion of males, current smokers, and current drinkers (P < 0.001; Table 1). During follow-up, all characteristics of hyperglycemic participants were different from those of participants without hyperglycemia (P < 0.05; Table S1).

Univariate analysis for hyperglycemia in the metabolically healthy population

Table S2 showed that higher age, BMI, FPG, DBP, SBP, TG, TC, LDL, AST, and ALT levels, current drinkers and smokers, and lower HDL-C level were the risk factors of hyperglycemia. Females had a lower risk of hyperglycemia than males. In Figure 2, the Kaplan–Meier curve showed that higher hazards were determined among MHOW and MHO (log-rank test, P < 0.001).

Association of MHOW/MHO and hyperglycemia risk among metabolically healthy participants

In metabolically healthy participants, 5,274 individuals developed hyperglycemia over 144,804 person-years of follow-up, and the overall rate of hyperglycemia was 36.42 per 1000 person-years. The rate of hyperglycemia was 29.35 in MHNW group, 54.07 in MHOW group, and 72.24 in MHO group per 1000 person-years, respectively.

The hazard ratio (HR) and 95% confidence intervals (CI) of the BMI categories on the incidence of hyperglycemia are listed in Table 2. In the crude model, compared with MHNW participants, the risk of hyperglycemia increased 85% in the MHOW group (HR = 1.85, 95% CI:1.75 to 1.97), and 163% in the MHO group (HR = 2.63, 95% CI:2.35 to 2.95), respectively. After adjusting for age, gender, and family history of diabetes, the risk of hyperglycemia in MHOW group and MHO group was still higher than in MHNW group. Furthermore, after adjusting for all the covariates, the relationship was not completely eliminated, with HRs (95% CI) of 1.23 (1.16–1.30) for MHOW and 1.49 (1.33–1.67) for MHO (*P* for trend < 0.001). Moreover, we analyzed the correlation between BMI as a continuous variable and the hyperglycemia risk. The risk of incident of hyperglycemia increased by 6% (HR = 1.06, 95% CI:1.04 to 1.07, P < 0.001) with 1 unit increase of BMI.

The restricted cubic spline model showed the risk of hyperglycemia increased gradually with increase in BMI, albeit in a nonlinear manner (*P* < 0.001, *P*-nonlinearity = 0.039, Figure S1).

Subgroup analyses and sensitivity analyses

The results of the stratified analyses and interaction effects are presented in Table 3. The additive interactions between MHOW/MHO and hyperglycemia risk were observed in gender, and stronger correlation was found in female participants. However, no significant interaction was found in age, height or family history of diabetes.

In addition, sensitivity analyses were performed for the risk of diabetes and IFG to confirm the robustness of our results (Table S3). After adjusting for covariates, the HR (95% CI) of incident diabetes was 1.39 (1.05-1.85) for MHOW and 2.91 (1.94-4.37) for MHO (*P* for trend <0.001); the HR (95% CI) of IFG was 1.23 (1.16-1.31) for MHOW and 1.49 (1.32-1.68) for MHO (*P* for trend <0.001). Furthermore, to verify the association of MHOW/MHO and hyperglycemia, the sensitivity analyses were performed as excluding the individuals with missing data of smoking and drinking status (n=12763, Table S4) or AST (n=19955, Table S5). The positive relationship of MHOW/MHO and hyperglycemia risk was still significant.

Discussion

The association between the BMI categories and incident hyperglycemia in the metabolically healthy population was examined in this cohort study. Compared to the MHNW group, both the MHOW and MHO groups exhibited a progressive increase in the risk of hyperglycemia, revealing a clear trend of rising hyperglycemia incidence with higher BMI. This present study suggests that the presence of MHOW/MHO, even with the absence of metabolic risk factors, significantly elevates the incidence of hyperglycemia. Consequently, MHOW and/or MHO should not be treated as a healthy status. Notably, weight management may serve as an effective strategy for preventing hyperglycemia and its related metabolic diseases among individuals with

MHOW or MHO.

The BioSHaRE-EU Healthy Obese Project have shown that the MHO prevalence of was 7%-28% for women, and 2%-19% for men [24]. The MHO prevalence ranged from 4.2% in a Chinese cohort [8] to 13.3% among Asian Indians [25] and 28.5% in African Americans [26]. In this study, the prevalence of MHOW (21.93%) and MHO (3.25%) were lower than previous reports, likely due to the strict definition of metabolically healthy status with none of metabolic abnormalities.

Wu et al. highlighted the positive effect of MHO on diabetes based on large numbers of epidemiological studies worldwide [6]. However, the correlation weakens when metabolically healthy status is strictly defined with none of metabolic abnormalities. Notably, the incidence of diabetes increased by 35-67% with one metabolic abnormality addition among metabolic healthy participants [27]. For example, Feng et al. found that the risk of diabetes increased among MHO individuals in a cohort of 49,702 older adults, but the association was not statistically significant when MHO was defined without ATP-III risk factors [11]. Similarly, Wei et al. observed an increased diabetes risk among MHO individuals, but this was not statistically significant among those with no metabolic abnormalities in the Dongfeng Tongji cohort study [12].

Despite these findings, our study identified a higher risk of hyperglycemia in the MHOW and MHO groups, even with the strict definition of metabolically healthy status as the absence of any metabolic abnormalities. Additionally, we found the positive association of MHOW/MHO phenotype on diabetes and IFG, respectively. In consistent, the risk of diabetes for MHOW or MHO individuals with no metabolic abnormalities was 1.89 and 3.88 times higher, respectively, than in MHNW young men [27]. These inconsistent results may be attributed to several factors. First, age differences may partly explain the variability in findings. The participants in previous studies had mean ages of 63.2 years [11] and 66 (63–71) years [12], whereas the mean age in our study was 40.95 ± 11.05 years. Younger MHO adults may present a higher hyperglycemia risk, as they are more likely to develop metabolic abnormalities in the short term. In contrast, middle-aged MHO individuals may have been overweight or obese for years without developing diabetes or metabolic disorders. Moreover, the concept of "metabolically healthy" status tends to diminish with aging [24], which likely accounts for the reduced prevalence of MHOW and MHO in earlier studies [11,12].

Notably, the interaction between gender and BMI categories on incident hyperglycemia was significant, with a higher risk observed in women than in men. This finding aligns with some studies [28, 29], but not all [30, 31]. For example, one cohort study found that the risk of diabetes and IFG was higher in obese women [28]. Similarly, another prospective case-cohort study noted a strong association between WC and type 2 diabetes mellitus, particularly in women [29]. However, the China Kadoorie Biobank study found greater hazard ratios for diabetes associated with BMI increments in men than in women (P for heterogeneity < 0.001) [31]. Previous studies have indicated that obesity is a more common and stronger risk factor for diabetes in women [32, 33].

The mechanism of positive association between BMI and hyperglycemia incidence in metabolic healthy population still remains unclear. However, it may be partly attributed to increased inflammation and insulin resistance associated with MHOW and/or MHO phenotypes. Overweight and obesity are known to induce chronic low-grade inflammation, particularly in insulin-sensitive tissues such as the liver, muscle, and adipose tissues [34]. Evidence suggests that chronic inflammation plays a critical role in diabetes development, even among MHO subjects [35, 36]. The accumulation and infiltration of pro-inflammatory macrophages in adipose tissue are significant contributors to chronic inflammation [37]. Pro-inflammatory cytokines, mainly secreted by macrophages, such as tumor necrosis factor (TNF-α) and interleukin-1 beta (IL-1β), can trigger various signaling pathways that induce insulin resistance. Key signaling pathways include TNF-α/IKKβ/NF-κB and TLR4/NLRP3/caspase-1/IL-1β, which impair insulin action and modulate pancreatic β-cell mass and function [38].

In addition, the prevalence of non-alcoholic fatty liver disease (NAFLD) is continually increasing due to the obesity epidemic [39]. NAFLD is not a consequence of insulin resistance, but it is also a key cause of insulin resistance or diabetes mellitus [40]. The high prevalence of NAFLD and visceral adiposity was found among the MHOW/MHO group, compared with the MHNW group [41]. In a MR analysis of data from the UK Biobank, the positive relationship of higher liver fat content and the risk of type 2 diabetes was observed [42]. Previous have shown that the increased hepatic lipogenesis and lipodystrophy-like phenotypes with visceral adiposity, resulted in dysregulated hepatokines and dysregulated adipokines, which might be the main cause of insulin resistance [40]. However, Wei et.al [12] found the association of the MHO phenotype and increased diabetes incidence did not differ by the presence or absence of NAFLD.

Study strengths and limitations

In addition to its large sample size and broad age range, this study has several strengths. Metabolically healthy individuals were included without any metabolic risk factors, allowing for the independent assessment of the role of BMI in hyperglycemia risk. Furthermore, sensitivity analyses, subgroup analyses, and interaction effects were examined to validate the reliability and stability of the results. However, there are several limitations to our study. First, WC was not measured at baseline, which prevented us from combining WC and BMI to distinguish individuals with abdominal obesity or predict the risk of hyperglycemia among those with abdominal obesity. Second, hyperglycemia prevalence may be underestimated, as random plasma glucose and/or postprandial plasma glucose levels were not collected. Finally, although numerous confounding factors were included, some potential factors may still be unaccounted for, such as physical activity, blood pressure-and lipids-lowing medicines and dietary habits.

Conclusion

In conclusion, this study demonstrated that MHOW and MHO are independently and positively associated with the risk of incident hyperglycemia in metabolically healthy adults, with a particularly strong correlation observed in women. Given the unsteady characteristics of metabolically healthy obese phenotypes, these findings underscore

the necessity of weight loss, increasing physical activity and diet quality management to reduce hyperglycemia risk and promote overall population health.

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Footnotes

Contributions

QG, QTY and SLJ: study design. QG, BYL, HML, RNX and YRX: data cleaning and analysis. QG, BYL, HML, RNX and YRX: result interpretation. QG: manuscript writing. BYL and HML: manuscript editing. All authors approved the final manuscript. Guarantor is QG.

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Competing interests: None declared.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data availability statement

The data used in this analysis can be accessed via the Dryad data repository at http://datadryad.org/withthedoi:10.5061/dryad.ft8750v.

Ethics statements

Patient consent: Not required.

Ethics approval: This study was approved by the Rich Healthcare Group Review Board, and the information was retrieved retrospectively.

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Table 1 Characteristics of study participants stratified by BMI group.

Variables	Total	MHNW	MHOW	MHO	*P*-value
N	47391	34920	10932	1539	
Age (years)	40.95 ± 11.05	40.10 ± 10.70	43.38 ± 11.60	42.93 ± 12.07	<0.001
Male, n (%)	22586 (47.66)	14124 (40.45)	7369 (67.41)	1093 (71.02)	<0.001
BMI (kg/m^2)	22.48 ± 2.59	21.25 ± 1.48	25.41 ± 1.05	29.56 ± 1.69	<0.001
FPG (mmol/L)	4.82 ± 0.52	4.78 ± 0.52	4.92 ± 0.52	4.99 ± 0.54	<0.001
SBP (mmHg)	110.88 ± 10.24	109.65 ± 10.30	114.07 ± 9.31	116.26 ± 8.63	<0.001
DBP (mmHg)	69.23 ± 7.47	68.45 ± 7.43	71.22 ± 7.14	72.63 ± 7.13	<0.001
TG (mmol/L)	0.92 ± 0.34	0.87 ± 0.32	1.06 ± 0.33	1.16 ± 0.32	<0.001
TC (mmol/L)	4.69 ± 0.80	4.65 ± 0.80	4.79 ± 0.80	4.84 ± 0.79	<0.001
HDL-C (mmol/L)	1.50 ± 0.26	1.53 ± 0.27	1.42 ± 0.23	1.38 ± 0.21	<0.001
LDL-C (mmol/L)	2.70 ± 0.62	2.66 ± 0.61	2.80 ± 0.62	2.85 ± 0.63	<0.001
ALT (mmol/L)	22.49 ± 10.50	21.66 ± 10.15	24.46 ± 10.94	27.46 ± 11.82	<0.001
AST (mmol/L)	20.22 ± 18.34	18.05 ± 16.65	25.39 ± 20.72	32.80 ± 23.65	<0.001
BUN (mmol/L)	4.63 ± 1.16	4.56 ± 1.14	4.84 ± 1.17	4.91 ± 1.13	<0.001
SCr (mmol/L)	68.87 ± 15.47	67.05 ± 14.79	73.92 ± 16.32	74.36 ± 14.91	<0.001
Smoking status, n (%)					<0.001
Current smoker	2049 (4.32)	1277 (3.66)	667 (6.10)	105 (6.82)	
Ever smoker	493 (1.04)	284 (0.81)	181 (1.66)	28 (1.82)	
Never smoker	10221 (21.57)	7600 (21.76)	2313 (21.16)	308 (20.01)	
Drinking status, n (%)					<0.001
Current drinker	249 (0.53)	144 (0.41)	85 (0.78)	20 (1.30)	
Ever drinker	2117 (4.47)	1274 (3.65)	740 (6.77)	103 (6.69)	
Never drinker	10397 (21.94)	7743 (22.17)	2336 (21.37)	318 (20.66)	
Family history of diabetes, n (%)					0.874
Yes	1061 (2.24)	789 (2.26)	239 (2.19)	33 (2.14)	

Table 2 Relationship between BMI categories and risk of hyperglycemia among metabolically healthy participants

	Case/N	Crude Model (HR, 95% CI)	Model I (HR, 95% CI)	Model II (HR, 95% CI)
Hyperglycemia				
BMI	5274/47391	1.14 (1.13, 1.15)	1.10 (1.09, 1.11)	1.06 (1.04, 1.07)
MHNW	3139/34920	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
MHOW	1798/10932	1.85 (1.75, 1.97)	1.51 (1.42, 1.60)	1.23 (1.16, 1.30)
MHO	337/1539	2.63 (2.35, 2.95)	2.10 (1.88, 2.36)	1.49 (1.33, 1.67)
P for trend		<0.001	<0.001	<0.001

Model I: adjusted for age, gender and family history of diabetes;
Model II: further adjusted for baseline FPG, ALT, AST, BUN, SCr, smoking status and drinking status.

Table 3 Multivariate-adjusted HR (95% CI) of hyperglycemia among BMI categories in stratified analyses

	MHNW	MHOW	MHO	*P* interaction
Gender				<0.001
Male	1.00 (Ref.)	1.11 (1.03, 1.20)	1.32 (1.15, 1.51)	
Female	1.00 (Ref.)	1.43 (1.29, 1.58)	1.88 (1.52, 2.32)	
Age (years)				0.534
< 40	1.00 (Ref.)	1.32 (1.17, 1.48)	1.51 (1.21, 1.89)	
≥ 40	1.00 (Ref.)	1.22(1.13, 1.31)	1.53 (1.34, 1.75)	
Family history of diabetes				0.290
yes	1.00 (Ref.)	1.23 (1.15, 1.30)	1.46 (1.30, 1.65)	
no	1.00 (Ref.)	1.05 (0.71, 1.55)	2.12 (1.07, 4.19)	
Height (cm)		1.31 (1.16, 1.47)	1.75 (1.38, 2.21)	0.056
≤ 161.90	1.00 (Ref.)	1.31 (1.16, 1.47)	1.75 (1.38, 2.21)	
162.00-169.90	1.00 (Ref.)	1.26 (1.13, 1.40)	1.33 (1.07, 1.64)	
≥ 170.00	1.00 (Ref.)	1.15 (1.04, 1.26)	1.50 (1.26, 1.78)	

Adjusted for gender (except gender subgroup), age (except age subgroup), family history of diabetes (except "family history of diabetes" subgroup), and baseline FPG, ALT, AST, BUN, SCr, smoking status and drinking status.

Figure legends:

Figure 1. Study flow chart.

Figure 2. Kaplan–Meier curves for cumulative hazard ratios of incident risk of hyperglycemia. The figure shows that the cumulative risk of incident hyperglycemia was markedly different among the BMI categories (log-rank test, $P < 0.001$) and increased gradually with increasing BMl, resulting in maximum risk of prediabetes in the MHO group.

Figure S1. Restricted cubic spline analyses ilustrating the dose-response relationshipbetween BMI and incidence of hyperglycemia.

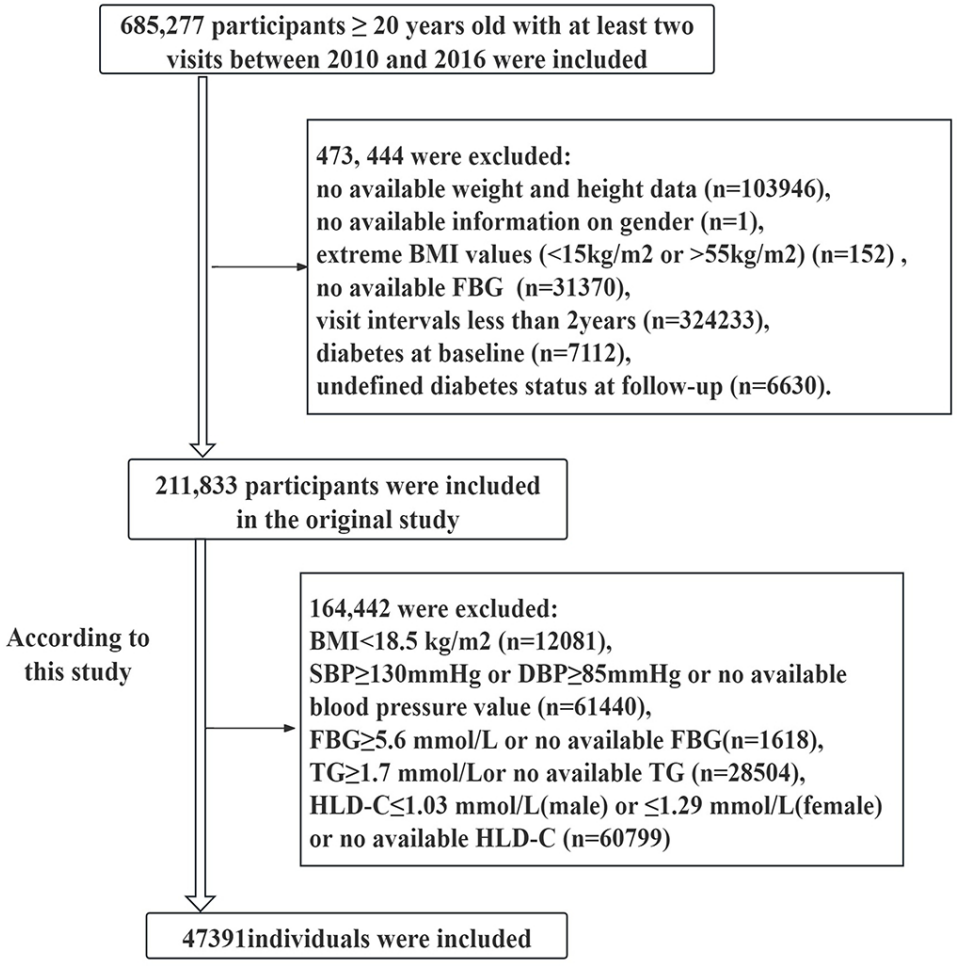

Figure 1. Study flow chart.

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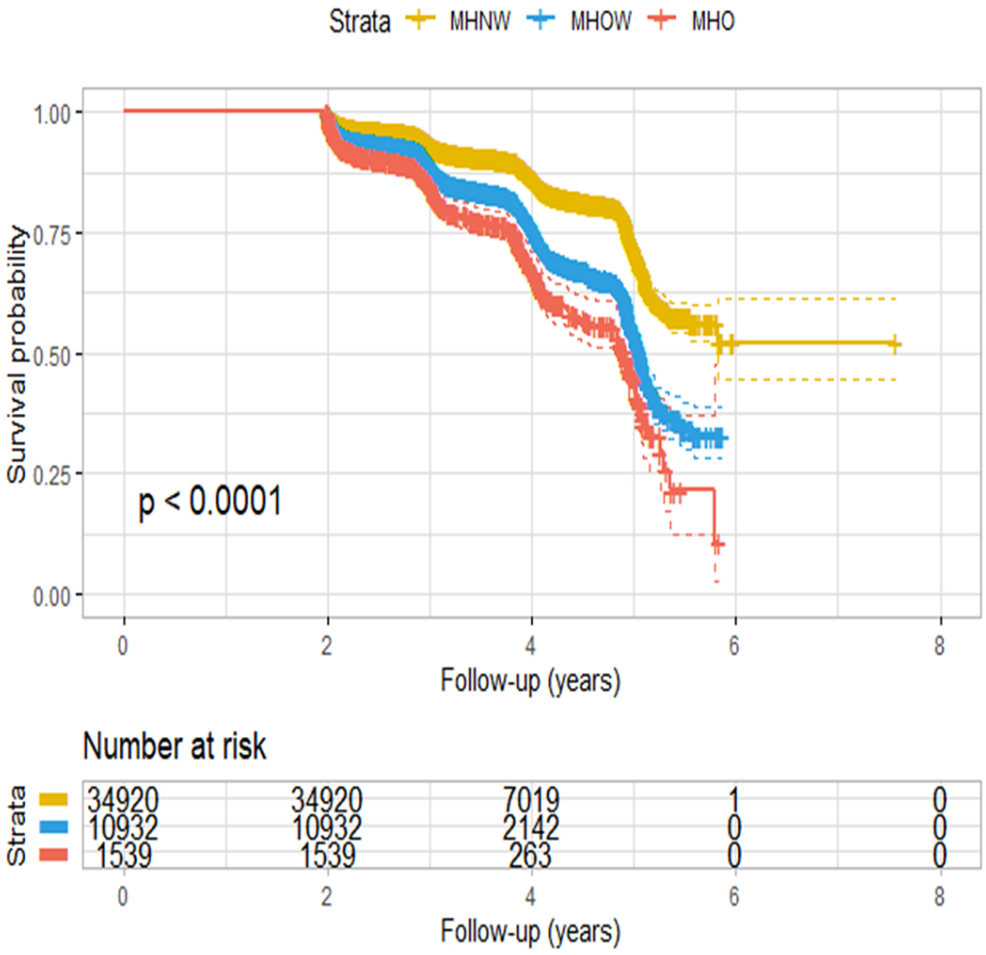

Figure 2. Kaplan–Meier curves for cumulative hazard ratios of incident risk of hyperglycemia. The figure shows that the cumulative risk of incident hyperglycemia was markedly different among the BMI categories (log-rank test, P < 0.001) and increased gradually with increasing BMI, resulting in maximum risk of prediabetes in the MHO group.

90x90mm (300 x 300 DPI)

Table S1
The characteristics of the study participants with/without hyperglycemia

Variables	Non-hyperglycemia	Hyperglycemia	*P*-value
N	42117	5274	
Age (years)	40.25 ± 10.66	46.54 ± 12.48	<0.001
Male, n (%)	19401 (46.06)	3185 (60.39)	<0.001
BMI (kg/m^2)	22.35 ± 2.53	23.48 ± 2.81	<0.001
FPG (mmol/L)	4.77 ± 0.51	5.20 ± 0.51	<0.001
SBP (mmHg)	110.53 ± 10.26	113.72 ± 9.70	<0.001
DBP (mmHg)	69.01 ± 7.48	70.95 ± 7.21	<0.001
TG (mmol/L)	0.91 ± 0.33	1.01 ± 0.34	<0.001
TC (mmol/L)	4.67 ± 0.80	4.83 ± 0.83	<0.001
HDL-C (mmol/L)	1.51 ± 0.26	1.46 ± 0.25	<0.001
LDL-C (mmol/L)	2.69 ± 0.62	2.79 ± 0.63	<0.001
ALT (mmol/L)	22.35 ± 10.46	23.63 ± 10.71	<0.001
AST (mmol/L)	19.89 ± 18.03	22.92 ± 20.38	<0.001
BUN (mmol/L)	4.60 ± 1.15	4.88 ± 1.18	<0.001
SCr (mmol/L)	68.44 ± 15.46	72.27 ± 15.09	<0.001
Smoking status, n (%)			<0.001
Current smoker	1741 (4.13)	308 (5.84)	
Ever smoker	441 (1.05)	52 (0.99)	
Never smoker	9171 (21.78)	1050 (19.91)	
Drinking status, n (%)			0.003
Current drinker	211 (0.50)	38 (0.72)	
Ever drinker	1844 (4.38)	273 (5.18)	
Never drinker	9298 (22.08)	1099 (20.84)	
Family history of diabetes, n (%)			0.039
Yes	922 (2.19)	139 (2.64)	

Table S 2
The results of univariate analysis for the risk factors of hyperglycemia

Covariables	HR (95%CI)	*P*-value
Age (years)	1.04 (1.03, 1.04)	<0.001
Gender		<0.001
Male	Ref.	
Female	0.60 (0.57, 0.64)	
FPG (mmol/L)	5.95 (5.63, 6.28)	<0.001
SBP (mmHg)	1.03 (1.03, 1.03)	<0.001
DBP (mmHg)	1.03 (1.02, 1.03)	<0.001
TG (mmol/L)	2.34 (2.17, 2.53)	<0.001
TC (mmol/L)	1.17 (1.13, 1.20)	<0.001
HDL-C (mmol/L)	0.62 (0.55, 0.68)	<0.001
LDL-C (mmol/L)	1.31 (1.26, 1.37)	<0.001
ALT (mmol/L)	1.00 (1.00, 1.00)	<0.001
AST (mmol/L)	1.01 (1.00, 1.01)	<0.001
BUN (mmol/L)	1.16 (1.14, 1.18)	<0.001
SCr (mmol/L)	1.01 (1.00, 1.01)	<0.001
Smoking status, n (%)		<0.001
Never smoker	Ref.	
Ever smoker	0.93 (0.70, 1.23)	
Current smoker	1.40 (1.23, 1.59)	
Drinking status, n (%)		<0.001
Never drinker	Ref.	
Ever drinker	1.15 (1.01, 1.31)	
Current drinker	1.56 (1.13, 2.15)	
Family history of diabetes		0.500
No	Ref.	
Yes	1.06 (0.90, 1.26)	

Table S3
Relationship between BMI categories and the risk of diabetes/IFG among the metabolically healthy participants

	Case/N	Crude Model (HR, 95% CI)	Model I (HR, 95% CI)	Model II (HR, 95% CI)
Diabetes				
BMI	239/47391	1.24 (1.20, 1.28)	1.19 (1.14, 1.24)	1.14 (1.09, 1.18)
MHNW	116/34920	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
MHOW	91/10932	2.53 (1.92, 3.32)	1.78 (1.35, 2.36)	1.39 (1.05, 1.85)
MHO	32/1539	6.84 (4.62, 10.11)	4.55 (3.05, 6.78)	2.91 (1.94, 4.37)
P for trend		<0.001	<0.001	<0.001
IFG				
BMI	5035/47152	1.14 (1.13, 1.15)	1.10 (1.09, 1.11)	1.05 (1.04, 1.07)
MHNW	3023/34804	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
MHOW	1707/10841	1.85 (1.74, 1.96)	1.51 (1.42, 1.61)	1.23 (1.16, 1.31)

MHO	305/1507	2.54 (2.26, 2.86)	2.07 (1.83, 2.33)	1.49 (1.32,1.68)
P for trend		<0.001	<0.001	<0.001

Model I: adjusted age, gender and the family history of diabetes;
Model II: further adjusted baseline FPG, ALT, AST, BUN, SCr, smoking status and drinking status.

Table S4
Relationship between BMI categories and the risk of hyperglycemia among the metabolically healthy participants without missing data of smoking and drinking status

	Case/N	Crude Model (HR, 95% CI)	Model I (HR, 95% CI)	Model II (HR, 95% CI)
BMI	1410/12763	1.12 (1.10, 1.14)	1.09 (1.07, 1.11)	1.05 (1.03, 1.07)
MHNW	844/9161	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
MHOW	485/3161	1.73 (1.55, 1.94)	1.43 (1.27, 1.60)	1.16 (1.03, 1.30)
MHO	81/441	2.14 (1.70, 2.69)	1.75 (1.39, 2.21)	1.28 (1.01, 1.61)
P for trend		<0.001	<0.001	<0.001

Model I: adjusted age, gender and the family history of diabetes;
Model II: further adjusted baseline FPG, ALT, AST, BUN, SCr, smoking status and drinking stat us.

Table S5
Relationship between BMI categories and the risk of hyperglycemia among the metabolically healthy participants without missing data of AST

	Case/N	Crude Model (HR, 95% CI)	Model I (HR, 95% CI)	Model II (HR, 95% CI)
BMI	2717/19955	1.14 (1.12, 1.15)	1.11 (1.09, 1.12)	1.05 (1.04, 1.07)
MHNW	1604/14558	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
MHOW	945/4742	1.85 (1.70, 2.01)	1.54 (1.42, 1.67)	1.23 (1.13, 1.34)
MHO	168/655	2.51 (2.15, 2.95)	2.06 (1.75, 2.46)	1.49 (1.27, 1.76)
P for trend		<0.001	<0.001	<0.001

Model I: adjusted for age, gender and family history of diabetes;

Model II: further adjusted for baseline FPG, ALT, AST, BUN, SCr, smoking status and drinking status.

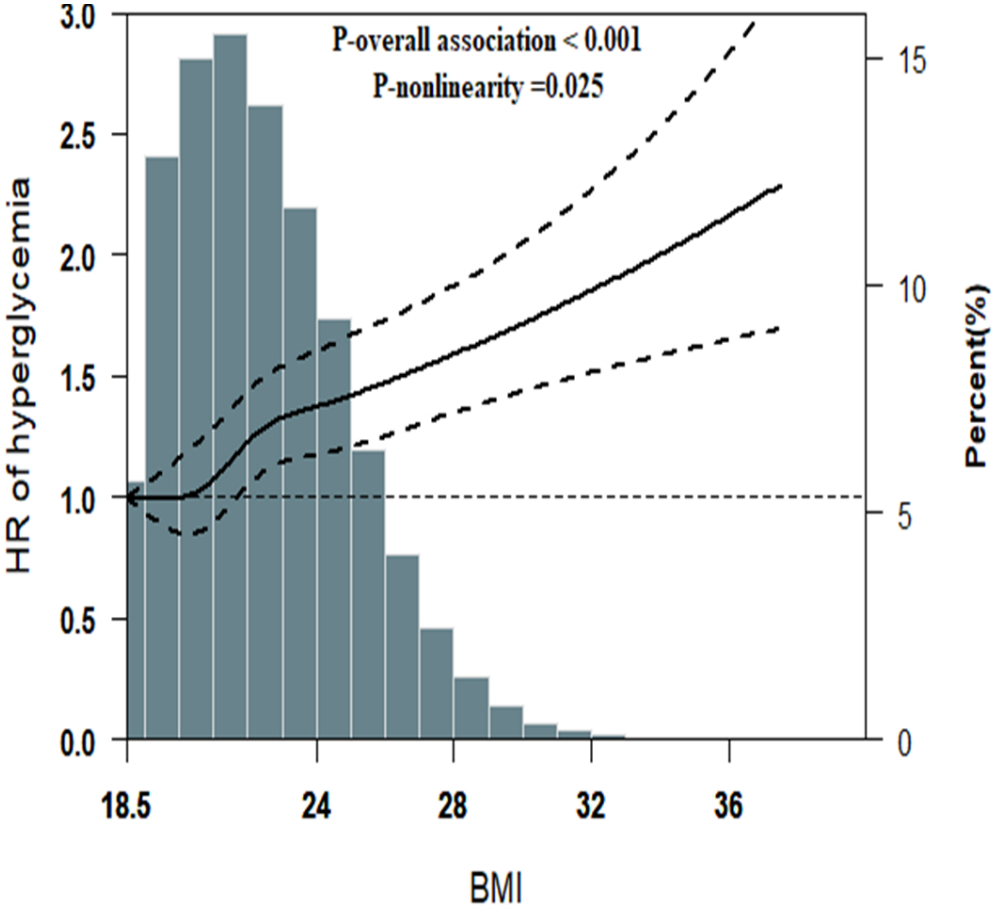

Figure S1. Restricted cubic spline analyses ilustrating the dose-response relationshipbetween BMI and incidence of hyperglycemia.

90x90mm (300 x 300 DPI)

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Metabolically healthy overweight/obesity with no metabolic abnormalities and incident hyperglycemia in Chinese adults: analysis of a retrospective cohort study

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Metabolically healthy overweight/obesity with no metabolic abnormalities and incident hyperglycemia in Chinese adults: analysis of a retrospective cohort study

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Abstract

Objectives: To explore whether metabolically healthy overweight (MHOW) and/or metabolically healthy obesity (MHO) increase hyperglycemia risk in a Chinese population with a board age range.

Design: Retrospective cohort study.

Setting: Secondary analysis of data from the DATADRYAD database, comprising health check records of participants from 32 regions and 11 cities in China between 2010 and 2016.

Participants: A total of 47391 metabolically healthy participants with none of metabolic abnormalities were selected.

Outcome measures: Hyperglycemia include incident diabetes and IFG. Diabetes was diagnosed with fasting blood glucose ≥7.0 mmol/L and typical clinical symptoms and/or on self-report during follow-up. The FPG level of IFG was from 5.6 to 6.9 mmol/L.

Results: With an average follow-up of 3.06 years, 5274 participants (11.13%) developed hyperglycemia over 144,804 person-years, with an incidence rate of 36.42 per 1000 persons-years. Adjusted model revealed a higher risk of incident hyperglycemia in the MHOW group (HR=1.23, 95%CIs: 1.16 to 1.30) and the MHO group (HR=1.49, 95% CI: 1.33 to 1.67) compared with the metabolic healthy normal weight group. With 1 unit increase of BMI, the risk of hyperglycemia increased by 6% (HR = 1.06, 95% CI: 1.04 to 1.07). The stratified analyses and interaction tests showed the robustness of the association, and there were a stronger association in women (*P* for interaction <0.001).

Conclusions: The MHOW and MHO phenotypes were positively associated with higher risk of hyperglycemia in this population. And the association was particularly stronger in women.

Strengths and limitations of this study

* This retrospective cohort study is representative of the Chinese population, featuring a large sample size and a broad age range.
* Metabolically healthy status was rigorously defined based on the NCEP ATP-III criteria with none of metabolic abnormalities.
* Waist circumference was not measured at baseline, limiting the ability to assess the risk of hyperglycemia in individuals with abdominal obesity.
* Missing information about blood pressure- and lipid-lowing medications may have interfered with appropriate exclusions from the MHOW/MHO groups.

INTRODUCTION

Approximately 537 million adults worldwide have been diagnosed with diabetes mellitus, with over 90% being type 2 diabetes mellitus [1]. In addition, prediabetes has emerged as a global epidemic. In 2021, 6.2% of the adult population had impaired fasting glucose (IFG), and 10.6% had impaired glucose tolerance [1]. Among Chinese adults, the prevalence of diabetes and prediabetes remained high and increased between 2013 and 2018 [2,3], with an estimated prevalence of 12.4% for diabetes and 38.1% for prediabetes in 2018 [3].

The global prevalence of obesity has been steadily rising since the early 1980s [4], which is one of the key risk factors for diabetes mellitus. However, some obese individuals, classified as having metabolically healthy obesity (MHO), do not present with major cardiovascular risk factors. Nonetheless, the MHO phenotype may progress to metabolically unhealthy obesity over time, increasing the risk of cardiovascular disease and mortality.

A critical issue is the inconsistency in defining MHO. The most common definition of MHO is fewer than two of criteria factors of the metabolic syndrome or fewer than one abnormal factor excluding waist circumference (WC) [5,6]. In 2021, Zembic A et.al have proposed a new definition of MHO based on systolic blood pressure, waist-to-hip ratio and diabetes, and found the cardiovascular mortality risk of the MHO group was not increased when compared the metabolic healthy normal weight (MHNW) individuals [7]. The estimated MHO prevalence was about 50% using ≤ 2 metabolic syndrome factors, or 24% using low HOMA-IR, or 13% when defined with no metabolic abnormality [8]. The relationship between MHO and the risk of diabetes remains a topic of interest. Some studies have suggested that MHO individuals are not at increased risk for diabetes compared to their MHNW counterparts [9, 10], while others have shown that MHO is indeed associated with a higher risk of diabetes [11, 12]. Moreover, when MHO is defined strictly with no metabolic abnormalities, the association with diabetes risk appears less significant [11, 12]. Recent studies have shown that the multi-organ insulin sensitivity in MHO group was lower than the metabolically healthy and lean group [13]. These inconsistent findings may be partly due to the differing age ranges studied, as most previous research focused on middle-aged individuals under 60 years [9, 10, 14-16], whereas studies in China predominantly examined older populations [11, 12, 17].

Therefore, we aimed to investigate the association between hyperglycemia (including diabetes and IFG) and metabolically healthy individuals without any metabolic abnormalities, based on ATP-III criteria, across young, middle-aged, and elderly groups in a large cohort of the Chinese population.

METHODS

Study design and participants

This study was conducted by the Rich Healthcare Group across 32 sites and 11 cities in China. The subjects who received a health check from 2010 to 2016 were recruited, and the demographic, lifestyle, medical history and family history of chronic disease were collected by questionnaire investigation. As a retrospective cohort study, 685277

participants were selected with at least two visits. After excluding the participant who meet the exclusion criteria, a total of 211833 participants (116123 male and 95710 female) were included (in Figure 1). The information of 211,833 individuals was introduced in detail, and the data were download from the "DATADRYAD" database (www.datadryad.org) by Chen et al. [18].

For this study, focusing on metabolically healthy status, we excluded participants with body mass index (BMI) < 18.5 kg/m² (n = 12,081); systolic blood pressure (SBP) ≥ 130 mmHg and/or diastolic blood pressure (DBP) ≥ 85 mmHg, or missing blood pressure values (n = 61,440); fasting plasma glucose (FPG) ≥ 5.6 mmol/L (n = 1,618); triglycerides (TG) ≥ 1.7 mmol/L or missing TG values (n = 28,504); or high-density lipoprotein cholesterol (HDL-C) ≤ 1.04 mmol/L (men) or ≤ 1.29 mmol/L (women) or missing HDL-C values (n = 60,799). A total of 47,391 individuals were included. The flowchart is shown in Figure 1.

Data collection

As described in the original study, basic information was collected via questionnaire, and anthropometric data were measured in a standardized manner. Blood pressure was measured using standard mercury sphygmomanometers. Fasting blood samples were collected to measure glucose, TG, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), HDL-C, aspartate transaminase (AST), and alanine transaminase (ALT) using an autoanalyzer (Beckman 5800).

Definitions of obesity and metabolic health

Body weight was categorized by BMI as follows: normal weight (18.5–23.9 kg/m²), overweight (24.0–27.9 kg/m²), and obese (≥ 28.0 kg/m²). WC was not used due to collinearity with BMI [15]. Metabolic health was defined according to the NCEP ATP-III criteria [5] as the absence of any metabolic abnormalities, which included: SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg; TG ≥ 1.7 mmol/L; FPG ≥ 5.6 mmol/L; and HDL-C ≤ 1.03 mmol/L in men or ≤ 1.29 mmol/L in women.

Based on BMI and metabolic health status, participants were classified into three phenotypes: (1) MHNW, (2) metabolically healthy overweight (MHOW), and (3) MHO.

Outcome measures

The primary of outcome was hyperglycemia, defined as a dichotomous variable (0 = non-hyperglycemia, 1 = hyperglycemia). In this study, hyperglycemia include incident diabetes and IFG. Diabetes was diagnosed with fasting blood glucose ≥7.0 mmol/L and typical clinical symptoms and/or self-report diabetes mellitus during follow-up. The FPG level of IFG was from 5.6 to 6.9 mmol/l based on the American Diabetes Association criteria [19].

Covariates

Covariates were selected based on previous literature[11, 12, 17, 18, 20, 21], and included continuous variables (age, ALT, AST, LDL-C, TC, blood urea nitrogen [BUN], and serum creatinine [SCr]) and categorical variables (gender, smoking status, drinking status, and family history of diabetes).

Missing data processing

Missing data were as follows: LDL-C: 26 (0.05%), ALT: 35 (0.07%), AST: 27433

(57.89%), BUN: 354 (0.75%), SCr: 113 (0.24%), drinking status: 34628 (73.07%), and smoking status: 34628 (73.07%), respectively. Multiple imputation was applied for missing continuous variables using a chained equation algorithm with the R's MI package. Missing categorical variables were treated as categorical in the analysis [22].

Statistical analysis

Basic characteristics were presented as mean ± SD or percentage. Group comparisons were conducted using one-way ANOVA or the Kruskal–Wallis test for continuous variables, and the χ^2 test for categorical variables. The Kaplan-Meier survival method and Cox-proportional hazard model were used to estimate the association of MHOW and MHO for incident hyperglycemia. According to the STROBE statement recommendation [23], the crude, minor- and full adjustment models were presented. In addition, a restricted cubic spline model was also constructed to assess the dose-response relationship between BMI and hyperglycemia risk.

Subgroup analyses were performed to assess the modifying effects of age, gender, height, and family history of diabetes on the association between BMI and hyperglycemia. Interaction tests were conducted between BMI categories and these subgroup variables. Sensitivity analyses were carried out to assess the robustness of the findings: 1) we did similar analysis after considering diabetes and IFG as separate outcomes; 2) we excluded the participants with missing smoking and drinking status.

All analyses were conducted using R software (version 4.3.3) and Empower Stats (version 4.1). A two-sided P-value < 0.05 was considered statistically significant.

Patient and public involvement

None.

RESULTS

Characteristics of the study participants

A total of 47391 metabolically healthy participants (47.66% male) were finally included. The mean age and BMI were 40.95± 11.05 years and 22.48±2.59 kg/m^2, respectively. During a follow-up period of 3.06 ± 0.95 years, 5,274 participants (11.13%) developed hyperglycemia. The characteristics stratified by BMI categories and the status of blood glucose are presented in Table 1 and Table S1. Participants with higher BMI generally had higher FPG, SBP, DBP, TG, TC, LDL-C, ALT, AST, BUN, and SCr levels, lower HDL-C level, and had a higher proportion of males, current smokers, and current drinkers ($P < 0.001$; Table 1). During follow-up, all characteristics of hyperglycemic participants were different from those of participants without hyperglycemia ($P < 0.05$; Table S1).

Univariate analysis for hyperglycemia in the metabolically healthy population

Table S2 showed that higher age, BMI, FPG, DBP, SBP, TG, TC, LDL, AST, and ALT levels, current drinkers and smokers, and lower HDL-C level were the risk factors of hyperglycemia. Females had a lower risk of hyperglycemia than males. In Figure 2, the Kaplan–Meier curve showed that higher hazards were determined among MHOW and MHO (log-rank test, $P < 0.001$).

Association of MHOW/MHO and hyperglycemia risk among metabolically healthy participants

In metabolically healthy participants, 5,274 individuals developed hyperglycemia over 144,804 person-years of follow-up, and the overall rate of hyperglycemia was 36.42 per 1000 person-years. The rate of hyperglycemia was 29.35 in MHNW group, 54.07 in MHOW group, and 72.24 in MHO group per 1000 person-years, respectively.

The hazard ratio (HR) and 95% confidence intervals (CI) of the BMI categories on the incidence of hyperglycemia are listed in Table 2. In the crude model, compared with MHNW participants, the risk of hyperglycemia increased 85% in the MHOW group (HR = 1.85, 95% CI:1.75 to 1.97), and 163% in the MHO group (HR = 2.63, 95% CI:2.35 to 2.95), respectively. After adjusting for age, gender, and family history of diabetes, the risk of hyperglycemia in MHOW group and MHO group was still higher than in MHNW group. Furthermore, after adjusting for all the covariates, the relationship was not completely eliminated, with HRs (95% CI) of 1.23 (1.16–1.30) for MHOW and 1.49 (1.33–1.67) for MHO (*P* for trend < 0.001). Moreover, we analyzed the correlation between BMI as a continuous variable and the hyperglycemia risk. The risk of incident of hyperglycemia increased by 6% (HR = 1.06, 95% CI:1.04 to 1.07, P < 0.001) with 1 unit increase of BMI.

The restricted cubic spline model showed the risk of hyperglycemia increased gradually with increase in BMI, albeit in a nonlinear manner (*P* < 0.001, *P*-nonlinearity = 0.039, Figure S1).

Subgroup analyses and sensitivity analyses

The results of the stratified analyses and interaction effects are presented in Table 3. The additive interactions between MHOW/MHO and hyperglycemia risk were observed in gender, and stronger correlation was found in female participants. However, no significant interaction was found in age, height or family history of diabetes.

In addition, sensitivity analyses were performed for the risk of diabetes and IFG to confirm the robustness of our results (Table S3). After adjusting for covariates, the HR (95% CI) of incident diabetes was 1.39 (1.05-1.85) for MHOW and 2.91 (1.94-4.37) for MHO (*P* for trend <0.001); the HR (95% CI) of IFG was 1.23 (1.16-1.31) for MHOW and 1.49 (1.32-1.68) for MHO (*P* for trend <0.001). Furthermore, to verify the association of MHOW/MHO and hyperglycemia, the sensitivity analyses were performed as excluding the individuals with missing data of smoking and drinking status (n=12763, Table S4) or AST (n=19955, Table S5). The positive relationship of MHOW/MHO and hyperglycemia risk was still significant.

DISCUSSION

The association between the BMI categories and incident hyperglycemia in the metabolically healthy population was examined in this cohort study. Compared to the MHNW group, both the MHOW and MHO groups exhibited a progressive increase in the risk of hyperglycemia, revealing a clear trend of rising hyperglycemia incidence with higher BMI. This present study suggests that the presence of MHOW/MHO, even with the absence of metabolic risk factors, significantly elevates the incidence of hyperglycemia. Consequently, MHOW and/or MHO should not be treated as a healthy status. Notably, weight management may serve as an effective strategy for

preventing hyperglycemia and its related metabolic diseases among individuals with MHOW or MHO.

The BioSHaRE-EU Healthy Obese Project have shown that the MHO prevalence of was 7%-28% for women, and 2%-19% for men [24]. The MHO prevalence ranged from 4.2% in a Chinese cohort [8] to 13.3% among Asian Indians [25] and 28.5% in African Americans [26]. In this study, the prevalence of MHOW (21.93%) and MHO (3.25%) were lower than previous reports, likely due to the strict definition of metabolically healthy status with none of metabolic abnormalities.

Wu et al. highlighted the positive effect of MHO on diabetes based on large numbers of epidemiological studies worldwide [6]. However, the correlation weakens when metabolically healthy status is strictly defined with none of metabolic abnormalities. Notably, the incidence of diabetes increased by 35-67% with one metabolic abnormality addition among metabolic healthy participants [27]. For example, Feng et al. found that the risk of diabetes increased among MHO individuals in a cohort of 49,702 older adults, but the association was not statistically significant when MHO was defined without ATP-III risk factors [11]. Similarly, Wei et al. observed an increased diabetes risk among MHO individuals, but this was not statistically significant among those with no metabolic abnormalities in the Dongfeng Tongji cohort study [12]. Despite these findings, our study identified a higher risk of hyperglycemia in the MHOW and MHO groups, even with the strict definition of metabolically healthy status as the absence of metabolic abnormalities. However, information about blood pressure- and lipid-lowing medication was missing, and some participants who used these medications would in fact be metabolically unhealthy and should have been excluded. This might partly interpret the positive association of MHOW/MHO and hyperglycemia risk, and the correlation needs to be furtherly explored.

Additionally, we found the positive association of MHOW/MHO phenotype on diabetes and IFG, respectively. In consistent, the risk of diabetes for MHOW or MHO individuals with no metabolic abnormalities was 1.89 and 3.88 times higher, respectively, than in MHNW young men [27]. These inconsistent results may be attributed to several factors. First, age differences may partly explain the variability in findings. The participants in previous studies had mean ages of 63.2 years [11] and 66 (63–71) years [12], whereas the mean age in our study was 40.95 ± 11.05 years. Younger MHO adults may present a higher hyperglycemia risk, as they are more likely to develop metabolic abnormalities in the short term. In contrast, middle-aged MHO individuals may have been overweight or obese for years without developing diabetes or metabolic disorders. Moreover, the concept of "metabolically healthy" status tends to diminish with aging [24], which likely accounts for the reduced prevalence of MHOW and MHO in earlier studies [11,12].

Notably, the interaction between gender and BMI categories on incident hyperglycemia was significant, with a higher risk observed in women than in men. This finding aligns with some studies [28, 29], but not all [30, 31]. For example, one cohort study found that the risk of diabetes and IFG was higher in obese women [28]. Similarly, another prospective case-cohort study noted a strong association between

WC and type 2 diabetes mellitus, particularly in women [29]. However, the China Kadoorie Biobank study found greater hazard ratios for diabetes associated with BMI increments in men than in women (P for heterogeneity < 0.001) [31]. Previous studies have indicated that obesity is a more common and stronger risk factor for diabetes in women [32, 33].

The mechanism of positive association between BMI and hyperglycemia incidence in metabolic healthy population still remains unclear. However, it may be partly attributed to increased inflammation and insulin resistance associated with MHOW and/or MHO phenotypes. Overweight and obesity are known to induce chronic low-grade inflammation, particularly in insulin-sensitive tissues such as the liver, muscle, and adipose tissues [34]. Evidence suggests that chronic inflammation plays a critical role in diabetes development, even among MHO subjects [35, 36]. The accumulation and infiltration of pro-inflammatory macrophages in adipose tissue are significant contributors to chronic inflammation [37]. Pro-inflammatory cytokines, mainly secreted by macrophages, such as tumor necrosis factor (TNF-α) and interleukin-1 beta (IL-1β), can trigger various signaling pathways that induce insulin resistance. Key signaling pathways include TNF-α/IKKβ/NF-κB and TLR4/NLRP3/caspase-1/IL-1β, which impair insulin action and modulate pancreatic β-cell mass and function [38].

In addition, the prevalence of non-alcoholic fatty liver disease (NAFLD) is continually increasing due to the obesity epidemic [39]. NAFLD is not a consequence of insulin resistance, but it is also a key cause of insulin resistance or diabetes mellitus [40]. The high prevalence of NAFLD and visceral adiposity was found among the MHOW/MHO group, compared with the MHNW group [41]. In a MR analysis of data from the UK Biobank, the positive relationship of higher liver fat content and the risk of type 2 diabetes was observed [42]. Previous have shown that the increased hepatic lipogenesis and lipodystrophy-like phenotypes with visceral adiposity, resulted in dysregulated hepatokines and dysregulated adipokines, which might be the main cause of insulin resistance [40]. However, Wei et.al [12] found the association of the MHO phenotype and increased diabetes incidence did not differ by the presence or absence of NAFLD.

Study strengths and limitations

In addition to its large sample size and broad age range, this study has several strengths. Metabolically healthy individuals were included without any metabolic risk factors, allowing for the independent assessment of the role of BMI in hyperglycemia risk. Furthermore, sensitivity analyses, subgroup analyses, and interaction effects were examined to validate the reliability and stability of the results. However, there are several limitations to our study. First, WC was not measured at baseline, which prevented us from combining WC and BMI to distinguish individuals with abdominal obesity or predict the risk of hyperglycemia among those with abdominal obesity. Second, the missing data on blood pressure- and lipid-lowering medications could have impacted the accuracy of the MHOW/MHO categories, as some participants on these medications may have been inappropriately considered metabolically healthy. Third, hyperglycemia prevalence may be underestimated, as random plasma glucose and/or postprandial plasma glucose levels were not collected. Finally, although

numerous confounding factors were included, some potential factors may still be unaccounted for, such as physical activity and dietary habits.

CONCLUSION

In conclusion, this study demonstrated that MHOW and MHO are independently and positively associated with the risk of incident hyperglycemia in metabolically healthy adults, with a particularly strong correlation observed in women. Given the unsteady characteristics of metabolically healthy obese phenotypes, these findings underscore the necessity of weight loss, increasing physical activity and diet quality management to reduce hyperglycemia risk and promote overall population health.

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Contributors

QG, QTY and SLJ: study design. QG, BYL, HML, RNX and YRX: data cleaning and analysis. QG, BYL, HML, RNX and YRX: result interpretation. QG: manuscript writing. BYL and HML: manuscript editing. All authors approved the final manuscript. Guarantor is QG.

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Competing interests

None declared.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

The data used in this analysis can be accessed via the Dryad data repository at http://datadryad.org/withthedoi:10.5061/dryad.ft8750v.

Patient consent

Not required.

Ethics approval

This study was approved by the Rich Healthcare Group Review Board, and the information was retrieved retrospectively.

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Table 1. Characteristics of study participants, stratified by BMI group

Variables	Total	MHNW	MHOW	MHO	*P*-value
N	47391	34920	10932	1539	
Age (years)	40.95 ± 11.05	40.10 ± 10.70	43.38 ± 11.60	42.93 ± 12.07	<0.001
Male, n (%)	22586 (47.66)	14124 (40.45)	7369 (67.41)	1093 (71.02)	<0.001
BMI (kg/m^2)	22.48 ± 2.59	21.25 ± 1.48	25.41 ± 1.05	29.56 ± 1.69	<0.001
FPG (mmol/L)	4.82 ± 0.52	4.78 ± 0.52	4.92 ± 0.52	4.99 ± 0.54	<0.001
SBP (mmHg)	110.88 ± 10.24	109.65 ± 10.30	114.07 ± 9.31	116.26 ± 8.63	<0.001
DBP (mmHg)	69.23 ± 7.47	68.45 ± 7.43	71.22 ± 7.14	72.63 ± 7.13	<0.001
TG (mmol/L)	0.92 ± 0.34	0.87 ± 0.32	1.06 ± 0.33	1.16 ± 0.32	<0.001
TC (mmol/L)	4.69 ± 0.80	4.65 ± 0.80	4.79 ± 0.80	4.84 ± 0.79	<0.001
HDL-C (mmol/L)	1.50 ± 0.26	1.53 ± 0.27	1.42 ± 0.23	1.38 ± 0.21	<0.001
LDL-C (mmol/L)	2.70 ± 0.62	2.66 ± 0.61	2.80 ± 0.62	2.85 ± 0.63	<0.001
ALT (mmol/L)	22.49 ± 10.50	21.66 ± 10.15	24.46 ± 10.94	27.46 ± 11.82	<0.001
AST (mmol/L)	20.22 ± 18.34	18.05 ± 16.65	25.39 ± 20.72	32.80 ± 23.65	<0.001
BUN (mmol/L)	4.63 ± 1.16	4.56 ± 1.14	4.84 ± 1.17	4.91 ± 1.13	<0.001
SCr (mmol/L)	68.87 ± 15.47	67.05 ± 14.79	73.92 ± 16.32	74.36 ± 14.91	<0.001
Smoking status, n (%)					<0.001

Current smoker	2049 (4.32)	1277 (3.66)	667 (6.10)	105 (6.82)	
Ever smoker	493 (1.04)	284 (0.81)	181 (1.66)	28 (1.82)	
Never smoker	10221 (21.57)	7600 (21.76)	2313 (21.16)	308 (20.01)	
Drinking status, n (%)					<0.001
Current drinker	249 (0.53)	144 (0.41)	85 (0.78)	20 (1.30)	
Ever drinker	2117 (4.47)	1274 (3.65)	740 (6.77)	103 (6.69)	
Never drinker	10397 (21.94)	7743 (22.17)	2336 (21.37)	318 (20.66)	
Family history of diabetes, n (%)					0.874
Yes	1061 (2.24)	789 (2.26)	239 (2.19)	33 (2.14)	

Table 2. Relationship between BMI categories and risk of hyperglycemia among metabolically healthy participants

	Case/N	Crude Model (HR, 95% CI)	Model I (HR, 95% CI)	Model II (HR, 95% CI)
Hyperglycemia				
BMI	5274/47391	1.14 (1.13, 1.15)	1.10 (1.09, 1.11)	1.06 (1.04, 1.07)
MHNW	3139/34920	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
MHOW	1798/10932	1.85 (1.75, 1.97)	1.51 (1.42, 1.60)	1.23 (1.16, 1.30)
MHO	337/1539	2.63 (2.35, 2.95)	2.10 (1.88, 2.36)	1.49 (1.33, 1.67)
P for trend		<0.001	<0.001	<0.001

Model I: adjusted for age, gender and family history of diabetes;
Model II: further adjusted for baseline FPG, ALT, AST, BUN, SCr, smoking status and drinking status.

Table 3. Multivariate-adjusted HR (95% CI) of hyperglycemia among BMI categories in stratified analyses

	MHNW	MHOW	MHO	*P* interaction
Gender				<0.001
Male	1.00 (Ref.)	1.11 (1.03, 1.20)	1.32 (1.15, 1.51)	
Female	1.00 (Ref.)	1.43 (1.29, 1.58)	1.88 (1.52, 2.32)	
Age (years)				0.534
< 40	1.00 (Ref.)	1.32 (1.17, 1.48)	1.51 (1.21, 1.89)	
≥ 40	1.00 (Ref.)	1.22(1.13, 1.31)	1.53 (1.34, 1.75)	
Family history of diabetes				0.290
yes	1.00 (Ref.)	1.23 (1.15, 1.30)	1.46 (1.30, 1.65)	
no	1.00 (Ref.)	1.05 (0.71, 1.55)	2.12 (1.07, 4.19)	
Height (cm)		1.31 (1.16, 1.47)	1.75 (1.38, 2.21)	0.056
≤ 161.90	1.00 (Ref.)	1.31 (1.16, 1.47)	1.75 (1.38, 2.21)	
162.00-169.90	1.00 (Ref.)	1.26 (1.13, 1.40)	1.33 (1.07, 1.64)	
≥ 170.00	1.00 (Ref.)	1.15 (1.04, 1.26)	1.50 (1.26, 1.78)	

Adjusted for gender (except gender subgroup), age (except age subgroup), family history of diabetes (except "family history of diabetes" subgroup), and baseline FPG, ALT, AST, BUN, SCr, smoking status and drinking status.

FIGURE LEGENDS

Figure 1. Study flowchart.

Figure 2. Kaplan–Meier curves for cumulative hazard ratios of incident risk of hyperglycemia. The figure shows that the cumulative risk of incident hyperglycemia was markedly different among the BMI categories (log-rank test, $P < 0.001$) and increased gradually with increasing BMl, resulting in maximum risk of prediabetes in the MHO group.

Suppelmentary Figure S1. Restricted cubic spline analyses ilustrating the dose-response relationshipbetween BMI and incidence of hyperglycemia.

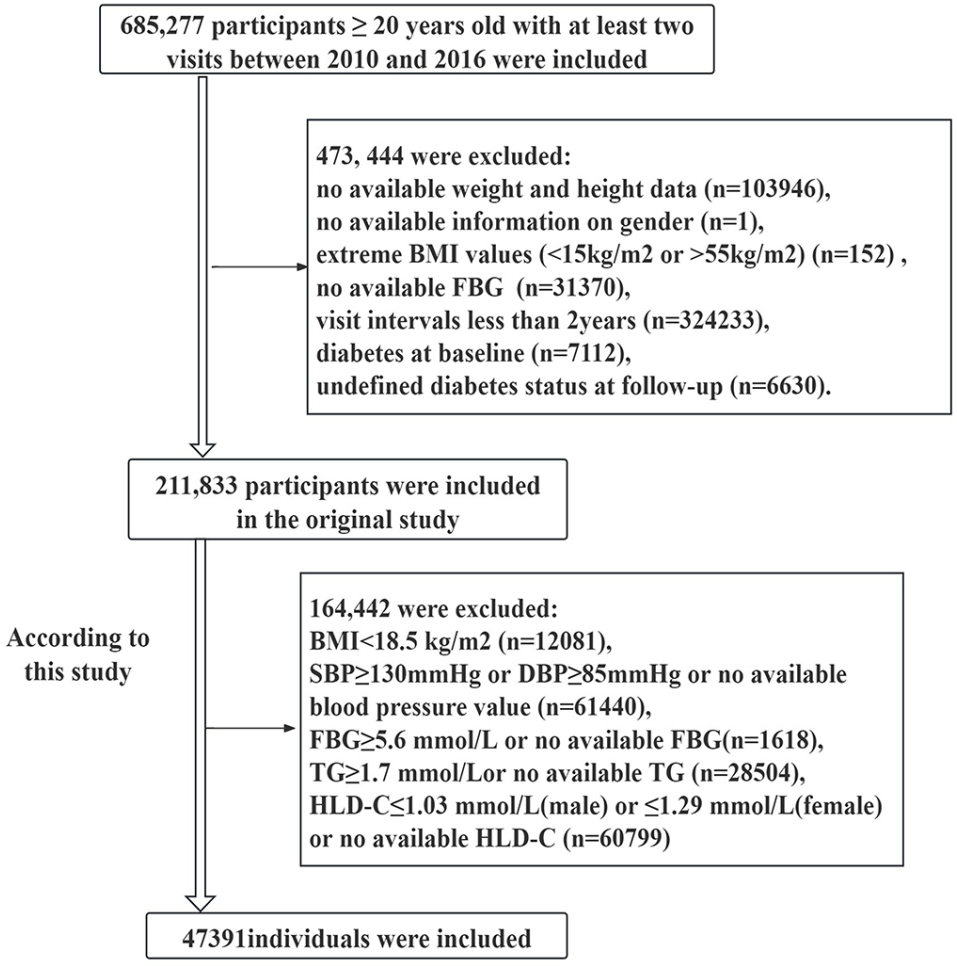

Figure 1. Study flow chart.

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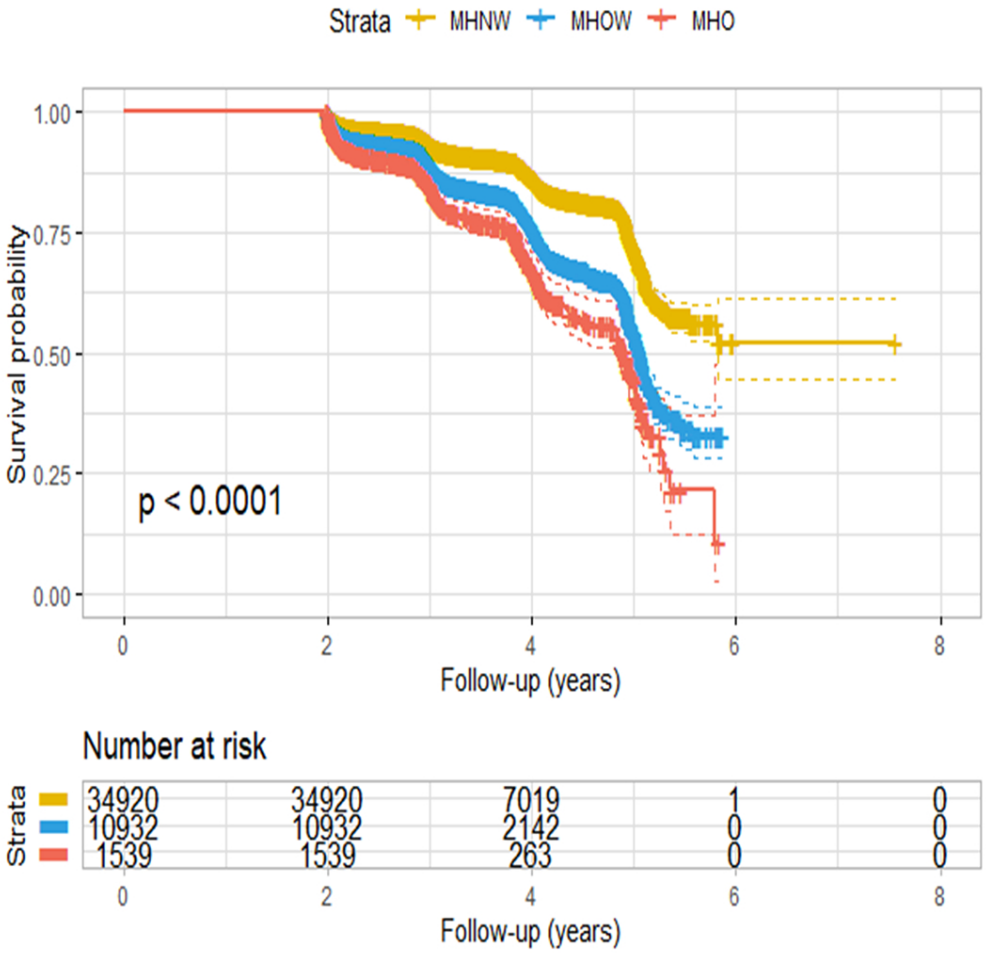

Figure 2. Kaplan–Meier curves for cumulative hazard ratios of incident risk of hyperglycemia. The figure shows that the cumulative risk of incident hyperglycemia was markedly different among the BMI categories (log-rank test, P < 0.001) and increased gradually with increasing BMI, resulting in maximum risk of prediabetes in the MHO group.

90x90mm (300 x 300 DPI)

Table S1
The characteristics of the study participants with/without hyperglycemia

Variables	Non-hyperglycemia	Hyperglycemia	*P*-value
N	42117	5274	
Age (years)	40.25 ± 10.66	46.54 ± 12.48	<0.001
Male, n (%)	19401 (46.06)	3185 (60.39)	<0.001
BMI (kg/m^2)	22.35 ± 2.53	23.48 ± 2.81	<0.001
FPG (mmol/L)	4.77 ± 0.51	5.20 ± 0.51	<0.001
SBP (mmHg)	110.53 ± 10.26	113.72 ± 9.70	<0.001
DBP (mmHg)	69.01 ± 7.48	70.95 ± 7.21	<0.001
TG (mmol/L)	0.91 ± 0.33	1.01 ± 0.34	<0.001
TC (mmol/L)	4.67 ± 0.80	4.83 ± 0.83	<0.001
HDL-C (mmol/L)	1.51 ± 0.26	1.46 ± 0.25	<0.001
LDL-C (mmol/L)	2.69 ± 0.62	2.79 ± 0.63	<0.001
ALT (mmol/L)	22.35 ± 10.46	23.63 ± 10.71	<0.001
AST (mmol/L)	19.89 ± 18.03	22.92 ± 20.38	<0.001
BUN (mmol/L)	4.60 ± 1.15	4.88 ± 1.18	<0.001
SCr (mmol/L)	68.44 ± 15.46	72.27 ± 15.09	<0.001
Smoking status, n (%)			<0.001
Current smoker	1741 (4.13)	308 (5.84)	
Ever smoker	441 (1.05)	52 (0.99)	
Never smoker	9171 (21.78)	1050 (19.91)	
Drinking status, n (%)			0.003
Current drinker	211 (0.50)	38 (0.72)	
Ever drinker	1844 (4.38)	273 (5.18)	
Never drinker	9298 (22.08)	1099 (20.84)	
Family history of diabetes, n (%)			0.039
Yes	922 (2.19)	139 (2.64)	

Table S 2
The results of univariate analysis for the risk factors of hyperglycemia

Covariables	HR (95%CI)	*P*-value
Age (years)	1.04 (1.03, 1.04)	<0.001
Gender		<0.001
Male	Ref.	
Female	0.60 (0.57, 0.64)	
FPG (mmol/L)	5.95 (5.63, 6.28)	<0.001
SBP (mmHg)	1.03 (1.03, 1.03)	<0.001
DBP (mmHg)	1.03 (1.02, 1.03)	<0.001
TG (mmol/L)	2.34 (2.17, 2.53)	<0.001
TC (mmol/L)	1.17 (1.13, 1.20)	<0.001
HDL-C (mmol/L)	0.62 (0.55, 0.68)	<0.001
LDL-C (mmol/L)	1.31 (1.26, 1.37)	<0.001
ALT (mmol/L)	1.00 (1.00, 1.00)	<0.001
AST (mmol/L)	1.01 (1.00, 1.01)	<0.001
BUN (mmol/L)	1.16 (1.14, 1.18)	<0.001
SCr (mmol/L)	1.01 (1.00, 1.01)	<0.001
Smoking status, n (%)		<0.001
Never smoker	Ref.	
Ever smoker	0.93 (0.70, 1.23)	
Current smoker	1.40 (1.23, 1.59)	
Drinking status, n (%)		<0.001
Never drinker	Ref.	
Ever drinker	1.15 (1.01, 1.31)	
Current drinker	1.56 (1.13, 2.15)	
Family history of diabetes		0.500
No	Ref.	
Yes	1.06 (0.90, 1.26)	

Table S3
Relationship between BMI categories and the risk of diabetes/IFG among the metabolically healthy participants

	Case/N	Crude Model (HR, 95% CI)	Model I (HR, 95% CI)	Model II (HR, 95% CI)
Diabetes				
BMI	239/47391	1.24 (1.20, 1.28)	1.19 (1.14, 1.24)	1.14 (1.09, 1.18)
MHNW	116/34920	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
MHOW	91/10932	2.53 (1.92, 3.32)	1.78 (1.35, 2.36)	1.39 (1.05, 1.85)
MHO	32/1539	6.84 (4.62, 10.11)	4.55 (3.05, 6.78)	2.91 (1.94, 4.37)
P for trend		<0.001	<0.001	<0.001
IFG				
BMI	5035/47152	1.14 (1.13, 1.15)	1.10 (1.09, 1.11)	1.05 (1.04, 1.07)
MHNW	3023/34804	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
MHOW	1707/10841	1.85 (1.74, 1.96)	1.51 (1.42, 1.61)	1.23 (1.16, 1.31)

MHO	305/1507	2.54 (2.26, 2.86)	2.07 (1.83, 2.33)	1.49 (1.32,1.68)
P for trend		<0.001	<0.001	<0.001

Model I: adjusted age, gender and the family history of diabetes;
Model II: further adjusted baseline FPG, ALT, AST, BUN, SCr, smoking status and drinking status.

Table S4
Relationship between BMI categories and the risk of hyperglycemia among the metabolically healthy participants without missing data of smoking and drinking status

	Case/N	Crude Model (HR, 95% CI)	Model I (HR, 95% CI)	Model II (HR, 95% CI)
BMI	1410/12763	1.12 (1.10, 1.14)	1.09 (1.07, 1.11)	1.05 (1.03, 1.07)
MHNW	844/9161	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
MHOW	485/3161	1.73 (1.55, 1.94)	1.43 (1.27, 1.60)	1.16 (1.03, 1.30)
MHO	81/441	2.14 (1.70, 2.69)	1.75 (1.39, 2.21)	1.28 (1.01, 1.61)
P for trend		<0.001	<0.001	<0.001

Model I: adjusted age, gender and the family history of diabetes;
Model II: further adjusted baseline FPG, ALT, AST, BUN, SCr, smoking status and drinking stat us.

Table S5
Relationship between BMI categories and the risk of hyperglycemia among the metabolically healthy participants without missing data of AST

	Case/N	Crude Model (HR, 95% CI)	Model I (HR, 95% CI)	Model II (HR, 95% CI)
BMI	2717/19955	1.14 (1.12, 1.15)	1.11 (1.09, 1.12)	1.05 (1.04, 1.07)
MHNW	1604/14558	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
MHOW	945/4742	1.85 (1.70, 2.01)	1.54 (1.42, 1.67)	1.23 (1.13, 1.34)
MHO	168/655	2.51 (2.15, 2.95)	2.06 (1.75, 2.46)	1.49 (1.27, 1.76)
P for trend		<0.001	<0.001	<0.001

Model I: adjusted for age, gender and family history of diabetes;

Model II: further adjusted for baseline FPG, ALT, AST, BUN, SCr, smoking status and drinking status.

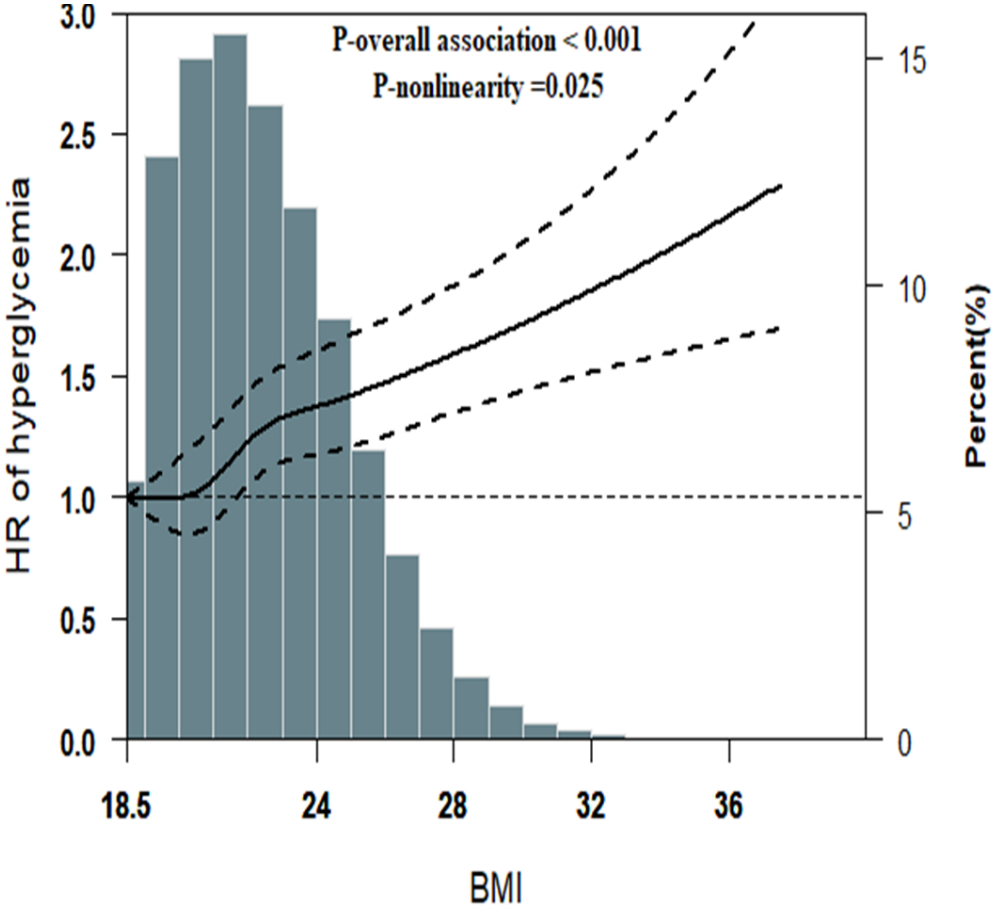

Figure S1. Restricted cubic spline analyses ilustrating the dose-response relationshipbetween BMI and incidence of hyperglycemia.

90x90mm (300 x 300 DPI)