# **BMJ Open** Metabolically healthy overweight/ obesity with no metabolic abnormalities and incident hyperglycaemia in Chinese adults: analysis of a retrospective cohort study Protected by copyright, including for uses related to

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#### ABSTRACT

**Objectives** To explore whether metabolically healthy overweight (MHOW) and/or metabolically healthy obesity (MHO) increase hyperglycaemia risk in a Chinese population with a broad 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 47 391 metabolically healthy participants with none of the metabolic abnormalities were selected.

Outcome measures Hyperglycaemia includes incident diabetes and impaired fasting glucose (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 fasting plasma glucose 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 hyperglycaemia over 144804 person-years, with an incidence rate of 36.42 per 1000 person-years. Adjusted model revealed a higher risk of incident hyperglycaemia in the MHOW group (HR=1.23, 95% Cls 1.16 to 1.30) and the MHO group (HR=1.49, 95% Cl 1.33 to 1.67) compared with the metabolically healthy normal weight group. With 1 unit increase of body mass index, the risk of hyperglycaemia 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 was a stronger association in women (p for interaction<0.001).

**Conclusions** The MHOW and MHO phenotypes were positively associated with a higher risk of hyperglycaemia in this population, and the association was particularly stronger in women.

#### **INTRODUCTION**

Approximately 537 million adults worldwide have been diagnosed with diabetes mellitus, with over 90% being type 2 diabetes mellitus.<sup>1</sup> In addition, pre-diabetes

#### STRENGTHS AND LIMITATIONS OF THIS STUDY

- $\Rightarrow$  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 the metabolic abnormalities.
- $\Rightarrow$  Waist circumference was not measured at baseline, limiting the ability to assess the risk of hyperglycaemia in individuals with abdominal obesity.
- ⇒ Missing information about blood pressure-lowering and lipid-lowering medications may have interfered with appropriate exclusions from the metabolically healthy overweight/metabolically healthy obesity groups.

Ing, has emerged as a global epidemic. In 2021, 6.2% of the adult population had impaired fasting glucose (IFG), and 10.6% faining discover tolerance.<sup>1</sup> Among Chinese adults, the prevalence of diabetes **9** and pre-diabetes remained high and increased between 2013 and 2018,<sup>23</sup> with an estimated prevalence of 12.4% for diabetes and 38.1% for pre-diabetes in 2018.<sup>3</sup>

The global prevalence of obesity has been steadily rising since the early 1980s,<sup>4</sup> which is one of the key risk factors for diabetes mellitus. However, some obese individuals, classified as having metabolically healthy obesity (MHO), 3 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 the criteria factors of the metabolic syndrome or fewer

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**Figure 1** Study flow chart. BMI, body mas index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HLD-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides.

than one abnormal factor excluding waist circumference (WC).<sup>56</sup> In 2021, Zembic 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 with the metabolic healthy normal weight (MHNW) individuals.<sup>7</sup> The estimated MHO prevalence was about 50% using  $\leq 2$ metabolic syndrome factors, 24% using low HOMA-IR or 13% when defined with no metabolic abnormality.<sup>8</sup> 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 with their MHNW counterparts,<sup>9 10</sup> while others have shown that MHO is indeed associated with a higher risk of diabetes.<sup>11 12</sup> Moreover, when MHO is defined strictly with no metabolic abnormalities, the association with diabetes risk appears less significant.<sup>11</sup><sup>12</sup> Recent studies have shown that the multiorgan insulin sensitivity in the MHO group was lower than the metabolically healthy and lean group.<sup>13</sup> These inconsistent findings may be partly due to the differing age ranges studied, as most previous research focused on middle-aged individuals under 60 vears,<sup>9 10 14-16</sup> whereas studies in China predominantly examined older populations.<sup>11 12 17</sup>

Therefore, we aimed to investigate the association between hyperglycaemia (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, 685 277 participants were selected with at least two visits. After excluding the participant who met the exclusion criteria, a total of 211 833 participants (116123 men and 95 710 women) were included (figure 1). The information of 211 833 individuals was introduced in detail, and the data were downloaded from the 'DATADRYAD' database (www.datadryad.org) by Chen *et al.*<sup>18</sup>

www.datadryad.org) by Chen *et al.*<sup>18</sup> For this study, focusing on metabolically healthy status, we excluded participants with body mass index (BMI) <18.5 kg/m<sup>2</sup> (n=12081); systolic blood pressure (SBP)  $\geq$ 130 mm Hg and/or diastolic blood pressure (DBP)  $\geq$ 85 mm Hg or missing blood pressure values (n=61 440); fasting plasma glucose (FPG)  $\geq$ 5.6 mmol/L (n=1618); triglycerides (TG)  $\geq$ 1.7 mmol/L or missing TG values (n=28504); or high-density lipoprotein cholesterol (HDL-C)  $\leq$ 1.04 mmol/L (men) or $\leq$ 1.29 mmol/L for (women) or missing HDL-C values (n=60 799). A total of 47 391 individuals were included. The flow chart is shown in figure 1.

#### **Data collection**

As described in the original study, basic information was collected via a questionnaire, and anthropometric data were measured in a standardised 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 autoanalyser (Beckman 5800).

#### Definitions of obesity and metabolic health

Body weight was categorised by BMI as follows: normal weight  $(18.5-23.9 \text{ kg/m}^2)$ , overweight  $(24.0-27.9 \text{ kg/m}^2)$  and obese ( $\geq 28.0 \text{ kg/m}^2$ ). WC was not used due to collinearity with BMI.<sup>15</sup> Metabolic health was defined according to the NCEP ATP-III criteria<sup>5</sup> as the absence of any metabolic abnormalities, which included: SBP  $\geq 130 \text{ mm}$  Hg and/or DBP  $\geq 85 \text{ mm}$  Hg; TG  $\geq 1.7 \text{ mmol/L}$ ; FPG  $\geq 5.6 \text{ mmol/L}$  and HDL-C $\leq 1.03 \text{ mmol/L}$  in men or  $\leq 1.29 \text{ mmol/L}$  in women.

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

#### **Outcome measures**

The primary outcome was hyperglycaemia, defined as a dichotomous variable (0=non-hyperglycaemia, 1=hyper-glycaemia). In this study, hyperglycaemia includes incident diabetes and IFG. Diabetes was diagnosed with fasting

blood glucose  $\geq 7.0$  mmol/L and typical clinical symptoms and/or self-reported 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.<sup>19</sup>

#### **Covariates**

Covariates were selected based on previous literature<sup>11</sup> <sup>12</sup> <sup>17</sup> <sup>18</sup> <sup>20</sup> <sup>21</sup> 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.<sup>22</sup>

#### **Statistical analysis**

Basic characteristics were presented as mean  $\pm$  SD or percentage. Group comparisons were conducted using one-way ANOVA or the Kruskal-Wallis test for continuous variables, and the  $\chi^2$  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 hyperglycaemia. According to the STROBE statement recommendation,<sup>23</sup> 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 hyperglycaemia 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 hyperglycaemia. Interaction tests were conducted between BMI categories and these subgroup variables. Sensitivity analyses were carried out to assess the robustness of the findings: (1) a similar analysis was performed after considering diabetes and IFG as separate outcomes and (2) the participants with missing smoking and drinking status or AST were excluded.

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

#### Patient and public involvement

Patients and/or the public were not involved in this study.

#### RESULTS

#### Characteristics of the study participants

A total of 47391 metabolically healthy participants (47.66% men) were finally included. The mean age and BMI were  $40.95\pm11.05$  years and  $22.48\pm2.59$  kg/m<sup>2</sup>, respectively. During a follow-up period of 3.06±0.95 years, 5274 participants (11.13%) developed hyperglycaemia. The characteristics stratified by BMI categories and the status of blood glucose are presented in table 1 and online supplemental 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 levels and had a higher proportion of men, current smokers and current drinkers (p<0.001; table 1). During follow-up, all characteristics of hyperglycaemic participants were different from those of participants without hyperglycaemia (p<0.05; online supplemental table S1).

#### Univariate analysis for hyperglycaemia in the metabolically healthy population

Protected by copyright, Online supplemental 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 levels were the risk factors of hyperglycaemia. Women had a lower risk of hyperglycaemia than men. In figure 2, the Kaplan-Meier curve showed that higher hazards were determined among MHOW and MHO (log-rank test, for uses related p<0.001).

#### Association of MHOW/MHO and hyperglycaemia risk among metabolically healthy participants

In metabolically healthy participants, 5274 individuals developed hyperglycaemia over 144804 person-years of đ follow-up, and the overall rate of hyperglycaemia was e 36.42 per 1000 person-years. The rate of hyperglycaemia and was 29.35 in the MHNW group, 54.07 in the MHOW group and 72.24 in the MHO group per 1000 persondata years, respectively.

The HR and 95% CI of the BMI categories on the inci-  $\blacksquare$ dence of hyperglycaemia are listed in table 2. In the crude model, compared with MHNW participants, the risk of ≥ hyperglycaemia increased by 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 ğ adjusting for age, gender and family history of diabetes, the risk of hyperglycaemia in the MHOW group and MHO group was still higher than in the MHNW group. Furthermore, after adjusting for all the covariates, the relationship was not completely eliminated, with HRs (95% CI) of 1.23 (1.16 to 1.30) for MHOW and 1.49 (1.33 to 1.67) for MHO (p for trend<0.001). Moreover, we analysed the correlation between BMI as a continuous variable and the hyperglycaemia risk. The risk of incident of & hyperglycaemia increased by 6% (HR=1.06, 95% CI 1.04 3 to 1.07, p<0.001) with 1 unit increase of BMI.

The restricted cubic spline model showed the risk of hyperglycaemia increased gradually with an increase in BMI, although in a nonlinear manner (p<0.001, P-nonlinearity=0.039, online supplemental figure S1).

#### Subgroup analyses and sensitivity analyses

The results of the stratified analyses and interaction effects are presented in table 3. The additive interactions

Table 1     Characteristics of study participants, stratified by BMI group							
Variables	Total	MHNW	MHOW	МНО	P value		
N	47 391	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/m²)	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 (mm Hg)	110.88±10.24	109.65±10.30	114.07±9.31	116.26±8.63	<0.001		
DBP (mm Hg)	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 (%)							
Yes	1061 (2.24)	789 (2.26)	239 (2.19)	33 (2.14)			

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; FPG, fasting plasma glucose: HDL-C, high-density lipoprotein cholesterol: LDL-C, low-density lipoprotein cholesterol: MHNW, metabolic healthy normal weight; MHO, metabolically healthy obesity; MHOW, metabolically healthy overweight; SBP, systolic blood pressure; SCr, serum creatinine; TC, total cholesterol; TG, triglycerides.

between MHOW/MHO and hyperglycaemia risk were observed in gender, and a 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 (online supplemental table S3). After adjusting for covariates, the HR (95% CI) of incident diabetes was 1.39 (1.05 to 1.85) for MHOW and 2.91 (1.94 to 4.37) for MHO (p for trend<0.001); the HR (95% CI) of IFG was 1.23 (1.16 to 1.31) for MHOW and 1.49 (1.32 to 1.68) for MHO (p for trend<0.001). Furthermore, to verify the association of MHOW/MHO and hyperglycaemia, the sensitivity analyses were performed as excluding the individuals with missing data on smoking and drinking status (n=12763, online supplemental table S4) or AST (n=19955, online supplemental table S5). The positive relationship of MHOW/MHO and hyperglycaemia risk was still significant.

#### DISCUSSION

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

The BioSHaRE-EU Healthy Obese Project has shown that the MHO prevalence was 7-28% for women and 2-19% for men.<sup>24</sup> The MHO prevalence ranged from 4.2% in a Chinese cohort <sup>8</sup> to 13.3% among Asian

Strata + MHNW + MHOW + MHO



**Figure 2** Kaplan-Meier curves for cumulative hazard ratios of incident risk of hyperglycaemia. The figure shows that the cumulative risk of incident hyperglycaemia was markedly different among the body mass index (BMI) categories (log-rank test, p<0.001) and increased gradually with increasing BMI, resulting in maximum risk of pre-diabetes in the metabolically healthy obesity (MHO) group. MHNW, metabolic healthy normal weight; MHOW, metabolically healthy overweight.

Indians<sup>25</sup> and 28.5% in African Americans.<sup>26</sup> In this study, the prevalence of MHOW (21.93%) and MHO (3.25%) was lower than that of previous reports, likely due to the strict definition of metabolically healthy status with none of the metabolic abnormalities.

Wu *et al* highlighted the positive effect of MHO on diabetes based on large numbers of epidemiological studies worldwide.<sup>6</sup> 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 the addition of

one metabolic abnormality among metabolically healthy participants.<sup>27</sup> For example, Feng *et al* found that the risk of diabetes increased among MHO individuals in a cohort of 49702 older adults, but the association was not statistically significant when MHO was defined without ATP-III risk factors.<sup>11</sup> 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.<sup>12</sup> Despite these findings, our study identified a higher risk **p** of hyperglycaemia 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-lowering and lipid-lowering medications 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 partly interpret the positive association of MHOW/MHO and hyperglycaemia risk, and the correlation needs to be further explored.

Additionally, we found the positive association of the MHOW/MHO phenotype with diabetes and IFG, ð respectively. In consistency, the risk of diabetes for MHOW or MHO individuals with no metabolic abnormalities was 1.89 and 3.88 times higher, respectively, ſe than in MHNW young men.<sup>27</sup> These inconsistent results than in MHNW young men.<sup>27</sup> 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<sup>11</sup> and 66 (63–71) years,<sup>12</sup> whereas the mean age in  $\square$ our study was 40.95±11.05 years. Younger MHO adults may present a higher hyperglycaemia 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 **a** developing diabetes or metabolic disorders. Moreover, the concept of 'metabolically healthy' status tends to training, and similar technologies diminish with ageing,<sup>24</sup> which likely accounts for the reduced prevalence of MHOW and MHO in earlier studies.<sup>11 12</sup>

Table 2     Relationship between BMI categories and the risk of hyperglycaemia among metabolically healthy participants							
	Case/N	Crude model (HR, 95% Cl)	Model I (HR, 95% CI)	Model II (HR, 95% CI)			
Hyperglycaemia							
BMI	5274/47 391	1.14 (1.13 to 1.15)	1.10 (1.09 to 1.11)	1.06 (1.04 to 1.07)			
MHNW	3139/34 920	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)			
MHOW	1798/10 932	1.85 (1.75 to 1.97)	1.51 (1.42 to 1.60)	1.23 (1.16 to 1.30)			
MHO	337/1539	2.63 (2.35 to 2.95)	2.10 (1.88 to 2.36)	1.49 (1.33 to 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.

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; FPG, fasting plasma glucose; MHNW, metabolic healthy normal weight; MHO, metabolically healthy obesity; MHOW, metabolically healthy overweight; SCr, serum creatinine.

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Toble 2 Multiveriet	to adjusted UR (05% CI) o	f hyperalyseemie among PMI o	atogorion in stratified analyses			
Table 3 Multivariate-adjusted RR (95% CI) of hypergrycaemia among BMI categories in stratified analyses						
	MHNW	MHOW	МНО	P interaction		
Gender				<0.001		
Male	1.00 (Ref.)	1.11 (1.03 to 1.20)	1.32 (1.15 to 1.51)			
Female	1.00 (Ref.)	1.43 (1.29 to 1.58)	1.88 (1.52 to 2.32)			
Age (years)				0.534		
<40	1.00 (Ref.)	1.32 (1.17 to 1.48)	1.51 (1.21 to 1.89)			
≥40	1.00 (Ref.)	1.22 (1.13 to 1.31)	1.53 (1.34 to 1.75)			
Family history of dia	betes			0.290		
Yes	1.00 (Ref.)	1.23 (1.15 to 1.30)	1.46 (1.30 to 1.65)			
No	1.00 (Ref.)	1.05 (0.71 to 1.55)	2.12 (1.07 to 4.19)			
Height (cm)		1.31 (1.16 to 1.47)	1.75 (1.38 to 2.21)	0.056		
≤161.90	1.00 (Ref.)	1.31 (1.16 to 1.47)	1.75 (1.38 to 2.21)			

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.

1.26 (1.13 to 1.40)

1.15 (1.04 to 1.26)

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; FPG, fasting plasma glucose; MHNW, metabolic healthy normal weight; MHO, metabolically healthy obesity; MHOW, metabolically healthy overweight; SCr, serum creatinine.

Notably, the interaction between gender and BMI categories on incident hyperglycaemia was significant, with a higher risk observed in women than in men. This finding aligns with some studies,<sup>28 29</sup> but not all.<sup>30 31</sup> For example, one cohort study found that the risk of diabetes and IFG was higher in obese women.<sup>28</sup> Similarly, another prospective case-cohort study noted a strong association between WC and type 2 diabetes mellitus, particularly in women.<sup>29</sup> 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).<sup>31</sup> Previous studies have indicated that obesity is a more common and stronger risk factor for diabetes in women.<sup>32 33</sup>

1.00 (Ref.)

1.00 (Ref.)

162.00-169.90

≥170.00

The mechanism of the positive association between BMI and hyperglycaemia 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 insulinsensitive tissues such as the liver, muscle and adipose tissues.<sup>34</sup> Evidence suggests that chronic inflammation plays a critical role in diabetes development, even among MHO subjects.<sup>35 36</sup> The accumulation and infiltration of pro-inflammatory macrophages in adipose tissue are significant contributors to chronic inflammation.<sup>37</sup> Proinflammatory cytokines, mainly secreted by macrophages, such as tumour necrosis factor (TNF- $\alpha$ ) and interleukin-1 beta (IL-1 $\beta$ ), can trigger various signalling pathways that induce insulin resistance. Key signalling pathways include TNF- $\alpha$ /IKK $\beta$ /NF- $\kappa$ B and TLR4/NLRP3/caspase-1/

IL-1β, which impair insulin action and modulate pancreatic  $\beta$ -cell mass and function.<sup>38</sup>

1.33 (1.07 to 1.64)

1.50 (1.26 to 1.78)

d to text In addition, the prevalence of non-alcoholic fatty liver disease (NAFLD) is continually increasing due to the obesity epidemic.<sup>39</sup> NAFLD is not only a consequence an of insulin resistance, but it is also a key cause of insulin resistance or diabetes mellitus.<sup>40</sup> The high prevalence of NAFLD and visceral adiposity was found among the MHOW/MHO group, compared with the MHNW group.<sup>41</sup> In an MR analysis of data from the UK Biobank, the positive relationship between higher liver fat content  $\triangleright$ and the risk of type 2 diabetes was observed.<sup>42</sup> Previous studies have shown that the increased hepatic lipogenesis and lipodystrophy-like phenotypes with visceral adiposity resulted in dysregulated hepatokines and dysregulated a adipokines, which might be the main cause of insulin resistance.<sup>40</sup> However, Wei *et al*<sup>12</sup> found the association of similar technolog 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 hyperglycaemia 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

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hyperglycaemia among those with abdominal obesity. Second, the missing data on blood pressure-lowering 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, hyperglycaemia 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 hyperglycaemia 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 hyperglycaemia risk and promote overall population health.

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**Contributors** QG, YT and SJ conceptualised the study design. QG, BL, HL, RX and YX performed the data cleaning and analysis. QG, BL, HL, RX and YX contributed to the result interpretation. QG contributed to the manuscript writing. BL and HL were involved in the manuscript editing. All authors approved the final manuscript. QG is the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

**Ethics approval** This study involves human participants and was approved by the Rich Healthcare Group Review Board. However, we are so sorry that the reference number or ID for the ethics approval was not obtainable according to the previous studies which used the same data.<sup>18, 43–45</sup> Given the retrospective nature of the study, participants were not informed consent to participate before taking part.

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Data availability statement Data are available in a public, open access repository. The data used in this analysis can be accessed via the Dryad data repository at http://datadryad.org/withthedoi:10.5061/dryad.ft8750v.

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