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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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| 4 | 1 | Association of metabolically healthy overweight/obesity with none of metabolic |
| 5 | 2 | abnormalities with incident hyperglycemia in Chinese adults: a 5-year cohort |
| 6 7 | 3 | study |
| 8 | 4 | Qin Gao ¹ , Boya Liang ² , Hongmin Li ¹ , Ruining Xie ¹ , Yaru Xu ³ , Yeqing Tong ^{4*} , |
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| 4 | 45 | Abstract |
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| 5 | 46 | Objectives: To explore whether metabolically healthy overweight (MHOW) and/or |
| 6 | 47 | metabolically healthy obesity (MHO) increase hyperglycemia risk in a Chinese |
| 7 | 48 | population with a board age range. |
| 8 | 49 | Design: Retrospective cohort study with health check from 2010 to 2016. |
| 9 10 | 50 | Setting and participants: A total of 47391 metabolically healthy participants with none |
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| 12 | 51 | of metabolic abnormalities were selected from 32 sites and 11 cities in China. Cox- |
| 13 | 52 | proportional hazard model was employed to estimate the association of MHOW and |
| 14 | 53 | MHO for incident hyperglycemia. |
| 15 16 | 54 | Primary and secondary outcome measures: hyperglycemia include incident diabetes |
| 17 | 55 | and IFG. Diabetes was diagnosed with fasting blood glucose \geq 7.0 mmol/L and/or on |
| 18 | 56 | self-report during follow-up. The FPG level of IFG was from 5.6 to 6.9 mmol/L. |
| 19 | 57 | Results: With an average follow-up of 3.06 years, 5274 participants (11.13%) |
| 20 | 58 | developed hyperglycemia over 144,804 person-years, with an incidence rate of 36.42 |
| 21 22 | 59 | per 1000 persons-years. Adjusted model revealed a higher risk of incident |
| 22 | 60 | hyperglycemia in the MHOW group (HR=1.23, 95%CIs: 1.16 to 1.30) and the MHO |
| 24 | | group (HR=1.49, 95% CI: 1.33 to 1.67) compared with the MHNW group. With 1 |
| 25 | 61 | |
| 26 | 62 | unit increase of BMI, the risk of hyperglycemia increased by 6% (HR = 1.06, 95% CI: |
| 27 | 63 | 1.04 to 1.07). The stratified analyses and interaction tests showed the robustness of |
| 28 29 | 64 | the association, and there were a stronger association in women (P for interaction |
| 30 | 65 | <0.001). |
| 31 | 66 | Conclusions: The MHOW and MHO phenotypes were positively associated with |
| 32 | 67 | higher risk of hyperglycemia in this population. And the association was particularly |
| 33 | 68 | stronger in women. Early screening and weight management can help lower the |
| 34 35 | 69 | hyperglycemia incidence in metabolically healthy population. |
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| 45 | 77 | Strengths and limitations of this study |
| 46 47 | 78 | 1. This retrospective cohort study was representative of Chinese population with a |
| 47 | 79 | large sample size and a broad age range. |
| 49 | 80 | 2. The metabolically healthy status was defined strictly based on NCEP ATP-III |
| 50 | 81 | criteria with none of metabolic abnormalities. |
| 51 | 82 | 3. The index of WC was not measured at baseline, we cannot predict the risk of |
| 52 53 | 83 | hyperglycemia among abdominally obese individuals. |
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| 55 | 84 05 | 4. The other confounding factors, such as physical activity and dietary factors were |
| 56 | 85 | not included in analysis. |
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89 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
2018³.

Global obesity prevalence increased gradually since the early 1980s⁴, 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

106 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 demographic⁷. 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 criteria⁸.

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}.

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

- 126 Methods
- 127 Subjects

Raw data were download from the "DATADRYAD" database (<u>www.datadryad.org</u>)
provided by Chen et al. ¹⁷. This secondary analysis did not violate the authors rights,
as the authors waived the copyright¹⁷.

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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/m² (n=12081); (2) systolic blood pressure (SBP) \geq 130 mmHg and/or diastolic blood pressure (DBP) \geq 85 mmHg or no available blood pressure value (n=61440); (3) fasting plasma glucose (FPG) \geq 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 $(18.5-23.9 \text{ kg/m}^2)$. overweight (24.0-27.9 kg/m²), and obese (≥ 28.0 kg/m²). WC was not used due to the collinearity with BMI¹⁴. Metabolically healthy status was defined based on NCEP ATP-III criteria⁵ as the absence of any metabolic abnormalities, which include: (1) systolic BP \geq 130 mmHg and/or diastolic BP \geq 85 mmHg; (2) TG \geq 1.7 mmol/L; (3) FPG \geq 5.6 mmol/L; (4) HDL-C \leq 1.03 mmol/L in men or \leq 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 criteria¹⁸.

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 \pm 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 recommendation²², 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/m², 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.

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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 = 1.85, 95% CI:1.75 to 1.97)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 men²³. The MHO prevalence ranged from 4.2% in a Chinese cohort⁸ to 13.3% among Asian Indians²⁴ and 28.5% in African Americans²⁵. 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

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numbers of epidemiological studies worldwide⁶. 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 participants²⁶. 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 factors¹¹. 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 study¹².

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 times²⁶. 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 years¹¹ and 66 (63-71) years¹², 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 aging²³, 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 higher²⁷. 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 study³⁰. 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 tissues³³. There was evidence showed that, even in MHO subjects, chronic inflammation plays critical role in diabetes development³⁴, ³⁵. Adipose tissue pro-inflammatory macrophages accumulation and infiltration was the most important cause of chronic inflammation³⁶. Pro-inflammatory cytokines

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307 mainly secreted from macrophages, such as tumor necrosis factor (TNF- α) and 308 interleukin-1 beta (IL-1 β), can trigger various signal pathway to induce insulin 309 resistance. Critical signal pathways include TNF- α / IKK β /NF- κ B, and TLR4/ 310 NLRP3/caspase-1/IL-1 β , which impair insulin action and modulate pancreas β -cell 311 mass and function³⁷.

10312Study strengths and limitations

11 Apart from a large sample size and a broad age range, this study has several strengths. 313 12 The metabolically healthy individuals were included without any metabolic risk 314 13 factors, as to reveal the independent role of BMI and hyperglycemia risk. Furtherly, 315 14 15 sensitivity analyses, subgroup analyses and interaction effects were examined to attest 316 16 the reliability and stability of the results. There are several limitations of our study. 317 17 Firstly, the index of WC was not measured at baseline, we cannot combine WC and 318 18 19 BMI to distinguish people with abdominally obesity and cannot predict the risk of 319 20 320 hyperglycemia among abdominally obese individuals. In addition, the hyperglycemia 21 321 prevalence may be underestimated as the random plasma glucose and/or postprandial 22 23 plasma glucose level were not collected. Finally, although numerous confounding 322 24 323 factors were included, some potential factors may exist, such as physical activity and 25 324 dietary factors. 26

To conclude, this study demonstrated that MHOW and MHO were independently 27 325 28 positively associated with risk of incident hyperglycemia in absolutely metabolically 326 29 healthy adults, and the correlation was particularly stronger in women. Considering 327 30 the unsteady characteristics of metabolically healthy/obese phenotypes, these findings 328 31 32 stress that early screening and weight control was necessary to lower hyperglycemia 329 33 330 risk and to promote population health. 34

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40 335 Footnotes

336 Contributions

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- ⁵⁵
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58349Data availability statement

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

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| 9 | 355 | Board, and the information was retrieved retrospectively. |
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| Μ | ge (years) | | MHNW | MHOW | MHO | P- |
|--------|----------------------|--------------------|--------------------|-------------------|-------------------|--------|
| A M | | | | | | value |
| Μ | ae (vears) | 47391 | 34920 | 10932 | 1539 | |
| | ge (years) | 40.95 ± 11.05 | 40.10 ± 10.70 | 43.38 ± 11.60 | 42.93 ± 12.07 | < 0.00 |
| | lale, n (%) | 22586 (47.66) | 14124 (40.45) | 7369 (67.41) | 1093 (71.02) | < 0.00 |
| B | $MI (kg/m^2)$ | 22.48 ± 2.59 | 21.25 ± 1.48 | 25.41 ± 1.05 | 29.56 ± 1.69 | < 0.00 |
| FI | PG (mmol/L) | 4.82 ± 0.52 | 4.78 ± 0.52 | 4.92 ± 0.52 | 4.99 ± 0.54 | < 0.00 |
| SI | BP (mmHg) | 110.88 ± 10.24 | 109.65 ± 10.30 | 114.07 ± 9.31 | 116.26 ± 8.63 | < 0.00 |
| D | BP (mmHg) | 69.23 ± 7.47 | 68.45 ± 7.43 | 71.22 ± 7.14 | 72.63 ± 7.13 | < 0.00 |
| T | G (mmol/L) | 0.92 ± 0.34 | 0.87 ± 0.32 | 1.06 ± 0.33 | 1.16 ± 0.32 | < 0.00 |
| T | C (mmol/L) | 4.69 ± 0.80 | 4.65 ± 0.80 | 4.79 ± 0.80 | 4.84 ± 0.79 | < 0.00 |
| Η | DL-C (mmol/L) | 1.50 ± 0.26 | 1.53 ± 0.27 | 1.42 ± 0.23 | 1.38 ± 0.21 | < 0.00 |
| L | DL-C (mmol/L) | 2.70 ± 0.62 | 2.66 ± 0.61 | 2.80 ± 0.62 | 2.85 ± 0.63 | < 0.00 |
| | LT (mmol/L) | 22.49 ± 10.50 | 21.66 ± 10.15 | 24.46 ± 10.94 | 27.46 ± 11.82 | < 0.00 |
| | ST (mmol/L) | 20.22 ± 18.34 | 18.05 ± 16.65 | 25.39 ± 20.72 | 32.80 ± 23.65 | < 0.00 |
| | UN (mmol/L) | 4.63 ± 1.16 | 4.56 ± 1.14 | 4.84 ± 1.17 | 4.91 ± 1.13 | < 0.00 |
| SC | Cr (mmol/L) | 68.87 ± 15.47 | 67.05 ± 14.79 | 73.92 ± 16.32 | 74.36 ± 14.91 | < 0.00 |
| | moking status, n (% | | | | | < 0.00 |
| | Current smoker | 2049 (4.32) | 1277 (3.66) | 667 (6.10) | 105 (6.82) | |
| ł | 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) | |
| | rinking status, n (% | · · · · · | | | | < 0.00 |
| | 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) | |
| | amily history of dia | · · · · · | (111) | | 010 (2000) | 0.874 |
| | Yes | 1061 (2.24) | 789 (2.26) | 239 (2.19) | 33 (2.14) | 0.071 |

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| nealthy participai | nts | | |
|--------------------|---|---|--|
| Case/N | Crude Model | Model I | Model II |
| | (HR, 95% CI) | (HR, 95% CI) | (HR, 95% CI) |
| ı | | | |
| 5274/47391 | 1.14 (1.13, 1.15) | 1.10 (1.09, 1.11) | 1.06 (1.04, 1.07) |
| 3139/34920 | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| 1798/10932 | 1.85 (1.75, 1.97) | 1.51 (1.42, 1.60) | 1.23 (1.16, 1.30) |
| 337/1539 | 2.63 (2.35, 2.95) | 2.10 (1.88, 2.36) | 1.49 (1.33, 1.67) |
| | < 0.001 | < 0.001 | < 0.001 |
| | Case/N a 5274/47391 3139/34920 1798/10932 | (HR, 95% CI) a 5274/47391 1.14 (1.13, 1.15) 3139/34920 1.00 (Ref.) 1798/10932 1.85 (1.75, 1.97) 337/1539 2.63 (2.35, 2.95) | Case/N Crude Model (HR, 95% CI) Model I (HR, 95% CI) a 5274/47391 1.14 (1.13, 1.15) 1.10 (1.09, 1.11) 3139/34920 1.00 (Ref.) 1.00 (Ref.) 1798/10932 1.85 (1.75, 1.97) 1.51 (1.42, 1.60) 337/1539 2.63 (2.35, 2.95) 2.10 (1.88, 2.36) |

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

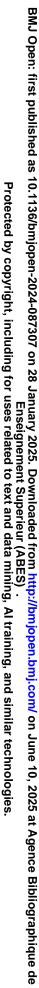
Model I: we adjusted age, gender and the family history of diabetes;

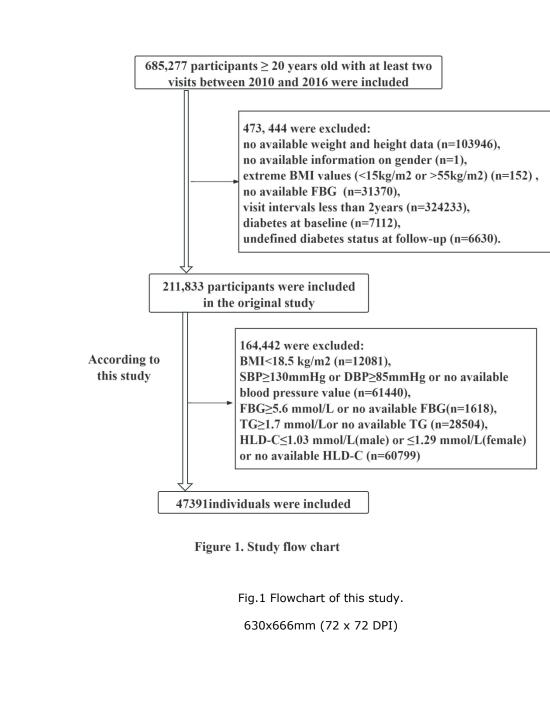
Model II: we further adjusted baseline FPG, ALT, AST, BUN, SCr, smoking status and drinking status.

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

| | MHNW | MHOW | МНО | 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) | |
| \geq 40 | 1.00 (Ref.) | 1.22 (1.13, 1.31) | 1.53 (1.34, 1.75) | |
| Family history | y 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.





1.00 -

Survival probability 0.50 0.50 0.25

0.00

Strata

0

ĬŃŎ

1539

0

Number at risk

p < 0.0001

2

34920 10932

1539

2

4

Follow-up (years)

7019 2142

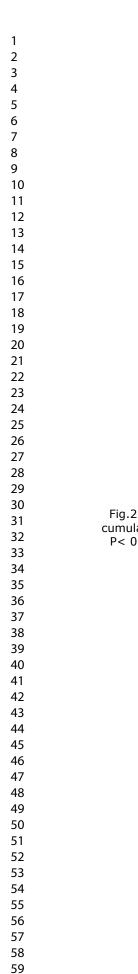
263

4

Follow-up (years)

MHO group.

173x128mm (96 x 96 DPI)



60

Strata + MHNW + MHOW + MHO 6 8 0 Ò ŏ ŏ ŏ 8 6 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

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| 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 diabete | es, n (%) | | 0.039 |
| Yes | 922 (2.19) | 139 (2.64) | |

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|----------|---------------------------------|----------------------------------|------------------|
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| 5 6 | Supplementary Table 2 | | |
| 7 | The results of univariate analy | usis for the risk factors of hyp | erolycemia |
| 8 | Covariables | HR (95%CI) | <i>P</i> -value |
| 9 10 | Age (years) | 1.04 (1.03, 1.04) | <0.001 |
| 11 | Gender | 1.04 (1.05, 1.04) | < 0.001 |
| 12 | Male | Ref. | ~0.001 |
| 13 | Female | 0.60 (0.57, 0.64) | |
| 14 15 | FPG (mmol/L) | 5.95 (5.63, 6.28) | < 0.001 |
| 16 | SBP (mmHg) | 1.03 (1.03, 1.03) | <0.001 <0.001 |
| 17 | (e / | | <0.001 <0.001 |
| 18 19 | DBP (mmHg) | 1.03 (1.02, 1.03) | |
| 20 | TG (mmol/L) | 2.34 (2.17, 2.53) | < 0.001 |
| 21 | TC (mmol/L) | 1.17 (1.13, 1.20) | < 0.001 |
| 22 | HDL-C (mmol/L) | 0.62 (0.55, 0.68) | < 0.001 |
| 23 24 | LDL-C (mmol/L) | 1.31 (1.26, 1.37) | < 0.001 |
| 25 | ALT (mmol/L) | 1.00 (1.00, 1.00) | < 0.001 |
| 26 | AST (mmol/L) | 1.01 (1.00, 1.01) | < 0.001 |
| 27 | BUN (mmol/L) | 1.16 (1.14, 1.18) | < 0.001 |
| 28 29 | SCr (mmol/L) | 1.01 (1.00, 1.01) | < 0.001 |
| 30 | Smoking status, n (%) | | < 0.001 |
| 31 | Never smoker | Ref. | |
| 32 | Ever smoker | 0.93 (0.70, 1.23) | |
| 33 34 | Current smoker | 1.40 (1.23, 1.59) | |
| 35 | Drinking status, n (%) | | < 0.001 |
| 36 | Never drinker | Ref. | |
| 37 | Ever drinker | 1.15 (1.01, 1.31) | |
| 38 39 | Current drinker | 1.56 (1.13, 2.15) | |
| 40 | Family history of diabetes | | 0.500 |
| 41 | No | Ref. | |
| 42 | Yes | 1.06 (0.90, 1.26) | |
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Supplementary Table 3

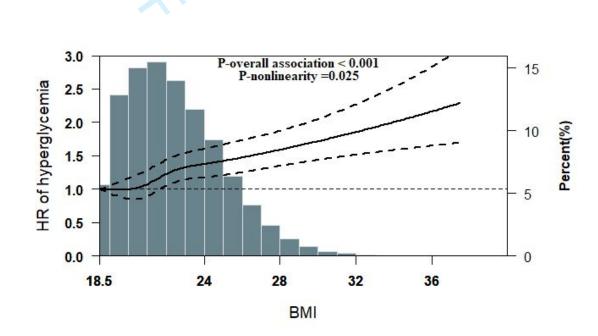
| | Case/N | Crude Model | Model I | Model II |
|-------------|------------|--------------------|--------------------|-------------------|
| | | (HR, 95% CI) | (HR, 95% CI) | (HR, 95% CI) |
| Diabetes | | | | |
| BMI | 239/47391 | 1.24 (1.20, 1.28) | 1.19 (1.14, 1.24) | 1.14 (1.09, 1.18) |
| MHNW | 116/34920 | 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 |

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

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.

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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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|--------------------------------------|---|
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| 3 | 1 | Metabolically healthy overweight/obesity with no metabolic abnormalities and |
| 4 | 2 | incident hyperglycemia in Chinese adults: analysis of a retrospective cohort |
| 5 6 | 2 | |
| 7 | | study |
| 8 | 4 | Qin Gao ¹ , Boya Liang ² , Hongmin Li ¹ , Ruining Xie ¹ , Yaru Xu ³ , Yeqing Tong ^{4*} , |
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45 Abstract

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

49 Design: Retrospective cohort study.

1050Setting: Secondary analysis of data from the DATADRYAD database, comprising1151health check records of participants from 32 regions and 11 cities in China between12522010 and 2016.

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

- 1055Primary and secondary outcome measures: hyperglycemia include incident diabetes1755Primary and secondary outcome measures: hyperglycemia include incident diabetes1856and IFG. Diabetes was diagnosed with fasting blood glucose \geq 7.0 mmol/L and typical1957clinical symptoms and/or on self-report during follow-up. The FPG level of IFG was2058from 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).
 - 68 Conclusions: The MHOW and MHO phenotypes were positively associated with 69 higher risk of hyperglycemia in this population. And the association was particularly 70 stronger in women.

- - 75 Strengths and limitations of this study
 - 76 1. This retrospective cohort study is representative of the Chinese population,77 featuring a large sample size and a broad age range.
 - 78 2. Metabolically healthy status was rigorously defined based on the NCEP ATP-III79 criteria with none of metabolic abnormalities.
 - 80 3. Waist circumference was not measured at baseline, limiting the ability to assess the
 81 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.
- 59 88

89 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.

97 The global prevalence of obesity has been steadily rising since the early 1980s ⁴, 98 which is one of the key risk factors for diabetes mellitus. However, some obese 99 individuals, classified as having metabolically healthy obesity (MHO), do not present 100 with major cardiovascular risk factors. Nonetheless, the MHO phenotype may 101 progress to metabolically unhealthy obesity over time, increasing the risk of 102 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 abnormality⁸. 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.

52 126 Methods

53 127 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

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- 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) \geq 130 mmHg and/or diastolic blood pressure (DBP) \geq 85 mmHg, or missing blood pressure values (n = 61,440); fasting plasma glucose (FPG) \geq 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.
- 19145Data 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).
- ²⁸ 152 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 BMI¹⁵. Metabolic health was defined according to the NCEP ATP-III criteria ⁵ as the absence of any metabolic abnormalities, which included: SBP \geq 130 mmHg and/or DBP \geq 85 mmHg; TG \geq 1.7 mmol/L; FPG \geq 5.6 mmol/L; and HDL-C \leq 1.03 mmol/L in men or \leq 1.29 mmol/L in women.
- 159 Based on BMI and metabolic health status, participants were classified into three
 160 phenotypes: (1) MHNW, (2) metabolically healthy overweight (MHOW), and (3)
 161 MHO.
- 41 162 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 criteria¹⁹.
- ⁵⁰ 169 Covariates
- ⁵¹ 170 Covariates were selected based on previous literature^{11, 12, 17, 18, 20, 21}, and included ⁵³ 171 continuous variables (age, ALT, AST, LDL-C, TC, blood urea nitrogen [BUN], and ⁵⁴ 172 serum creatinine [SCr]) and categorical variables (gender, smoking status, drinking ⁵⁵ status, and family history of diabetes).
- 57 174 Missing Data Processing
- 58175Missing data were as follows: LDL-C: 26 (0.05%), ALT: 35 (0.07%), AST: 2743359176(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.

181 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 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.
- ³² 199 **Patient and public involvement**
 - 200 None.
- ³⁴ 200 None. 35 201 **Results**

³⁶ 202 **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/m², 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).

⁵⁰₅₁ 213 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

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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.

24 237 The restricted cubic spline model showed the risk of hyperglycemia increased 26 238 gradually with increase in BMI, albeit in a nonlinear manner (P < 0.001, P-27 239 nonlinearity = 0.039, Figure S1).

28 240 Subgroup analyses and sensitivity analyses 29 240 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.

48 255 **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

³/₄ 265 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 men²⁴. 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}.

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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-a) and interleukin-1 beta (IL- 1β), can trigger various signaling pathways that induce insulin resistance. Key signaling pathways include TNF- α /IKK β /NF- κ B and TLR4/NLRP3/caspase-1/IL-1 β , 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

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| 3 4 | 352 | the necessity of weight loss, increasing physical activity and diet quality management |
| 5 | 353 | to reduce hyperglycemia risk and promote overall population health. |
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| 17 | | |
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| 30 | 372 | Data availability statement |
| 31 | 373 | The data used in this analysis can be accessed via the Dryad data repository at |
| 32 | 374 | http://datadryad.org/withthedoi:10.5061/dryad.ft8750v. |
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| 35 | 376 | Patient consent: Not required. |
| 36 | 377 | Ethics approval: This study was approved by the Rich Healthcare Group Review |
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| 13 | BMI (kg/m |
| 14 | FPG (mmo |
| 15 | SBP (mmH |
| 16 | DBP (mmF |
| 17 | TG (mmol/ |
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| 19 | TC (mmol/ |
| 20 | HDL-C (m |
| 21 | LDL-C (mi |
| 22 | ALT (mmo |
| 23 | AST (mmo |
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| 6 | Table 1 Characteristics | of study participat | nts stratified by | BMI group. |
|---|-------------------------|---------------------|-------------------|------------|
| 7 | Variables | Total | MHNW | MHO |

| Variables | Total | MHNW | MHOW | MHO | <i>P</i> - |
|-----------------------|---------------------------------------|------------------------|-------------------|-------------------|------------|
| | | | | | value |
| Ν | 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 | $\sim 21.66 \pm 10.15$ | 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 (% | · · · · · · · · · · · · · · · · · · · | Ň. | , | | < 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 di | | × / | | × / | 0.874 |
| Yes | 1061 (2.24) | 789 (2.26) | 239 (2.19) | 33 (2.14) | |

| healthy partic | ipants | | | |
|----------------|------------|-------------------|-------------------|-------------------|
| | Case/N | Crude Model | Model I | Model II |
| | | (HR, 95% CI) | (HR, 95% CI) | (HR, 95% CI) |
| Hyperglycem | a | | | |
| 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 |

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

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

| stratified analyses | | | | |
|---------------------|-------------|-------------------|-------------------|----------------------|
| | MHNW | MHOW | MHO | <i>P</i> interaction |
| Gender | | 6 | | < 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) | |
| \geq 40 | 1.00 (Ref.) | 1.22(1.13, 1.31) | 1.53 (1.34, 1.75) | |
| Family history of c | liabetes | | | 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) | |

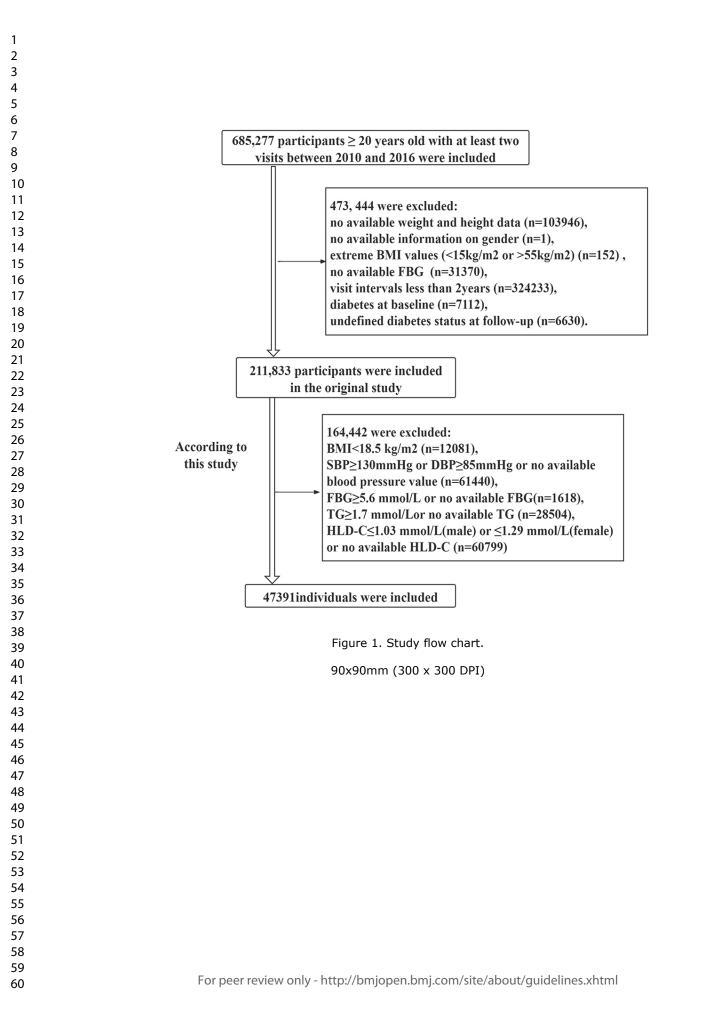
Adjusted for gender (except gender subgroup), age (except age subgroup), family history of diabetes (except "family history of diabetes" subgroup), and baseline FPG, ALT, AST, BUN, SCr, smoking status and drinking status.

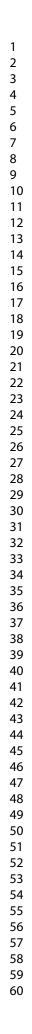
Figure legends:

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 BMI, 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.





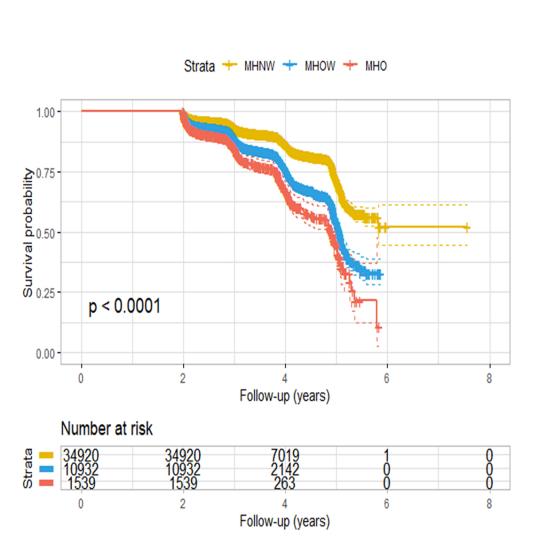


Figure 2. Kaplan–Meier curves for cumulative hazard ratios of incident risk of hyperglycemia. The figure shows that the cumulative risk of incident hyperglycemia was markedly different among the BMI categories (log-rank test, P < 0.001) and increased gradually with increasing BMI, resulting in maximum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

90x90mm (300 x 300 DPI)

| Variables | Non-hyperglycemia | Hyperglycemia | P-value |
|--------------------------|--------------------|-------------------|---------|
| Ν | 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 diabe | etes, n (%) | | 0.039 |
| Yes | 922 (2.19) | 139 (2.64) | |

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The results of univariate analysis for the risk factors of hyperglycemia

| Covariables | HR (95%CI) | <i>P</i> -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

| participants | | | | | |
|--------------|------------|--------------------|-------------------|-------------------|--|
| | Case/N | Crude Model | Model I | Model II | |
| | | (HR, 95% CI) | (HR, 95% CI) | (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) | |
| МНО | 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. |
|--------------------|----------|-----------------------|--|------------------|
| <i>P</i> for trend | | <0.001 | <0.001 | < 0.001 |
| | | and the family histor | ry of diabetes; (, BUN, SCr, smoking) | status and drink |
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Table S4

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

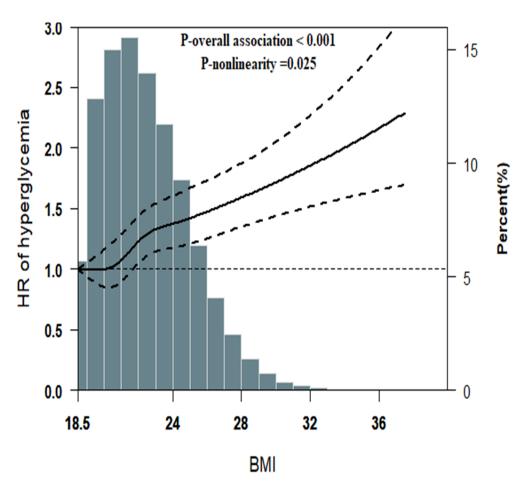
| | Case/N | Crude Model | Model I | Model II |
|-------------|------------|-------------------|-------------------|-------------------|
| | | (HR, 95% CI) | (HR, 95% CI) | (HR, 95% CI) |
| BMI | 1410/12763 | 1.12 (1.10, 1.14) | 1.09 (1.07, 1.11) | 1.05 (1.03, 1.07) |
| MHNW | 844/9161 | 1.00 (Ref.) | 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 |

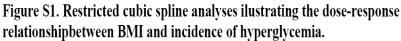
Table S5

| participants w | ithout missing da | ta of smoking and drink | ing status | | 7 |
|--------------------|--------------------|---|------------------------|--------------------------|--|
| | Case/N | Crude Model | Model I | Model II | rote |
| | | (HR, 95% CI) | (HR, 95% CI) | (HR, 95% CI) |)cte |
| BMI | 1410/12763 | 1.12 (1.10, 1.14) | 1.09 (1.07, 1.11) | 1.05 (1.03, 1.07) | d by |
| MHNW | 844/9161 | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) | cop |
| MHOW | 485/3161 | 1.73 (1.55, 1.94) | 1.43 (1.27, 1.60) | 1.16 (1.03, 1.30) | yrig |
| МНО | 81/441 | 2.14 (1.70, 2.69) | 1.75 (1.39, 2.21) | 1.28 (1.01, 1.61) | ht, i |
| P for trend | | <0.001 | < 0.001 | < 0.001 | nclu |
| 5 | 0,0 | r and the family histo seline FPG, ALT, AS | T, BUN, SCr, smoking | status and drinking stat | Protected by copyright, including for uses related to text and data mining, Al training, and similar techn |
| Table S5 | | | | | ıg, ar |
| - | | - | of hyperglycemia among | the metabolically health | ıy <mark>ıd</mark> |
| participants v | vithout missing da | | | | mila |
| | Case/N | Crude Model | Model I | Model II | r tec |
| | 0717/10055 | (HR, 95% CI) | (HR, 95% CI) | (HR, 95% CI) | hno |
| BMI | 2717/19955 | 1.14 (1.12, 1.15) | 1.11 (1.09, 1.12) | 1.05 (1.04, 1.07) | ologies. |
| MHNW | 1604/14558 | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) | ies. |
| 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) | |
| <i>P</i> for trend | | < 0.001 | < 0.001 | < 0.001 | |
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Model I: adjusted for age, gender and family history of diabetes;

| Model status. | II: further | adjusted | for baselin | e FPG, | ALT, A | ST, BUN | , SCr, | smoking | status ar |
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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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| 3 | 1 | Metabolically healthy overweight/obesity with no metabolic abnormalities and |
| 4 | 2 | incident hyperglycemia in Chinese adults: analysis of a retrospective cohort |
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| 6 7 | 3 | study |
| 7 8 | 4 | Qin Gao ¹ , Boya Liang ² , Hongmin Li ¹ , Ruining Xie ¹ , Yaru Xu ³ , Yeqing Tong ^{4*} , |
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Abstract 45 46 **Objectives:** To explore whether metabolically healthy overweight (MHOW) and/or metabolically healthy obesity (MHO) increase hyperglycemia risk in a Chinese 47 population with a board age range. 48 49 Design: Retrospective cohort study. 50 Setting: Secondary analysis of data from the DATADRYAD database, comprising health check records of participants from 32 regions and 11 cities in China between 51 2010 and 2016. 52 Participants: A total of 47391 metabolically healthy participants with none of 53 metabolic abnormalities were selected. 54

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

Results: With an average follow-up of 3.06 years, 5274 participants (11.13%) 59 developed hyperglycemia over 144,804 person-years, with an incidence rate of 36.42 60 61 per 1000 persons-years. Adjusted model revealed a higher risk of incident 62 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 63 weight group. With 1 unit increase of BMI, the risk of hyperglycemia increased by 6% 64 (HR = 1.06, 95% CI: 1.04 to 1.07). The stratified analyses and interaction tests 65 showed the robustness of the association, and there were a stronger association in 66 women (*P* for interaction <0.001). 67

68 **Conclusions:** The MHOW and MHO phenotypes were positively associated with 69 higher risk of hyperglycemia in this population. And the association was particularly 70 stronger in women.

75 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.

97 The global prevalence of obesity has been steadily rising since the early 1980s ⁴, 98 which is one of the key risk factors for diabetes mellitus. However, some obese 99 individuals, classified as having metabolically healthy obesity (MHO), do not present 100 with major cardiovascular risk factors. Nonetheless, the MHO phenotype may 101 progress to metabolically unhealthy obesity over time, increasing the risk of 102 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 abnormality⁸. 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.

51 126

127 METHODS

128 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

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- 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) \geq 130 mmHg and/or diastolic blood pressure (DBP) ≥ 85 mmHg, or missing blood pressure values (n = 61,440); fasting plasma glucose (FPG) \geq 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) $\leq 1.04 \text{ mmol/L}$ (men) or $\leq 1.29 \text{ mmol/L}$ (women) or missing HDL-C values (n = 60,799). A total of 47,391 individuals were included. The flowchart is shown in Figure 1.

20
21146Data 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 BMI¹⁵. 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 \geq 85 mmHg; TG \geq 1.7 mmol/L; FPG \geq 5.6 mmol/L; and HDL-C \leq 1.03 mmol/L in men or \leq 1.29 mmol/L in women. Based on BMI and metabolic health status, participants were classified into three
- 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

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 criteria¹⁹.
- 51 170 **Covariates**
- 171 Covariates were selected based on previous literature^{11, 12, 17, 18, 20, 21}, and included
 172 continuous variables (age, ALT, AST, LDL-C, TC, blood urea nitrogen [BUN], and
 173 serum creatinine [SCr]) and categorical variables (gender, smoking status, drinking
 174 status, and family history of diabetes).
- 58 175 Missing data processing
- ⁵⁹ 176 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.

181 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 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.

190 Subgroup analyses were performed to assess the modifying effects of age, gender, 191 height, and family history of diabetes on the association between BMI and 192 hyperglycemia. Interaction tests were conducted between BMI categories and these 193 subgroup variables. Sensitivity analyses were carried out to assess the robustness of 194 the findings: 1) we did similar analysis after considering diabetes and IFG as separate 195 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**
- 199 None.

RESULTS

202 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/m², 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).

⁵⁰ 213 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

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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 men²⁴. 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

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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-1B), 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 epidemic³⁹. 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.

42 339 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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| 11 502 easloffice@easloffice.eu; European Association for the Study of Diabetes (EASD); 12 503 European Association for the Study of Obesity (EASO); European Association for the 14 504 Study of the Liver (EASL): EASL-EASD-EASO Clinical Practice Guidelines on the 14 505 management of metabolic dysfunction-associated steatotic liver disease (MASLD). J 16 507 40. Stefan N, Schick F, Birkenfeld AL, Härnig HU, White MF. The role of hepatokines in 508 NAFLD. Cell Metab. 2023;35(2):236-52. doi:10.1016/j.emet.2023.01.006 509 41. Stefan N, Schick F, Birkenfeld AL, Härnig HU, White MF. The role of hepatokines in 508 NAFLD. Cell Metab. 2023;3(2):236-52. doi:10.1016/j.emet.2023.01.006 509 41. Stefan N, Schick F, Birkenfeld AL, Härnig HU, White MF. The role of hepatokines in 508 NAFLD. Cell Metab. 2017;07:008 Cell Metab. 2017;26(2):292-300. 512 42. Mattin S, Storkin EP, Thomas EL, et al. Estimating the Effect of Liver and Pancreas 513 Volume and Fat Content on Risk of Diabetes: A Mendelian Randomization Study. Diabetes Care. 2022;45(2):460-8. doi:10.2337/dc21-1262 516 520 516 521 521 521 523 518 519 514 | | | | | • | • | | 200. |
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| 504 Study of the Liver (EASL). EASL-EASD Clinical Practice Guidelines on the 15 505 management of metabolic dysfunction-associated steatotic liver disease (MASLD). J 16 506 Hepatol. 2024;81(3):492-542. doi:10.1016/j.jhep.2024.04.031 17 507 40. Stefan N, Schick F, Birkendel AL, Härng HU, White MF. The role of hepatokines in 18 507 40. Stefan N, Schick F, Birkendel AL, Härng HU, White MF. The role of hepatokines in 10 S08 NAFLD. Cell Metab. 2023;35(2):236-52. doi:10.1016/j.cmet.2023.01.006 509 10 Metabolically Unhealthy Normal Weight in Humans. Cell Metab. 2017;26(2):292-300. 511 doi:10.1016/j.cmet.2017.07.008 21 42. Martin S, Sorokin EP, Thomas EL, et al. Estimating the Effect of Liver and Pancreas 513 Volume and Fat Content on Risk of Diabetes: A Mendelian Randomization Study. Table 1. Characteristics of study participants, stratified by BMI group Variables Total MHNW MHOW Pator Mitor Total MHNW MHO value Table 1. Characteristics of study participants, stratified by BMI group Variable | 504 Study of the Liver (EASL). EASD-EASD Clinical Practice Guidelines on the 15 505 management of metabolic dysfunction-associated steatotic liver disease (MASLD). J 16 506 Hepatol. 2024;81(3):492-542. doi:10.1016/j.jhep.2024.04.031 17 507 40. Stefan N, Schick F, Birkenfeld AL, Häring HU, White MF. The role of hepatokines in 17 Stefan N, Schick F, Birkenfeld AL, Häring HU, Waite MF. The role of hepatokines in 18 Stefan N, Schick F, Birkenfeld AL, Häring HU, Waite MF. The role of hepatokines in 19 Stefan N, Schick F, Birkenfeld AL, Häring HU, Waite MF. The role of hepatokines in 19 Stefan N, Schick F, Birkenfeld AL, Häring HU, Waite MF. The role of hepatokines in 10 Metabolically Unhealthy Normal Weight in Humans. Cell Metab. 2017;26(2):292-300. Stift of Study participants, stratified by BMI group Volume and Fat Content on Risk of Diabetes: A Mendelian Randomization Study. Stift Stift Stift Stift Stift Stift Stift Stift | | | 0 | · • | • | | |
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| 19 508 NAFLD. Cell Metab. 2023;35(2):236-52. doi:10.1016/j.cmet.2023.01.006 20 509 41. Stefan N, Schick F, Haring HU. Causes, Characteristics, and Consequences of Metabolically Unhealthy Normal Weight in Humans. Cell Metab. 2017;26(2):292-300. doi:10.1016/j.cmet.2017.07.008 21 42. Martin S, Sorokin EP, Thomas EL, et al. Estimating the Effect of Liver and Pancreas Volume and Fat Content on Risk of Diabetes: A Mendelian Randomization Study. Diabetes Care. 2022;45(2):460-8. doi:10.2337/dc21-1262 28 516 517 30 518 518 31 519 518 32 518 522 7 512 40.95 ± 11.05 40.10 ± 10.70 43.38 ± 11.60 42.93 ± 12.07 <0.001 41 Male, n (%) 22.586 (47.66) 14124 (40.45) 7369 (67.41) 1093 (71.02) <0.001 43 Male, n (%) 22.586 (47.66) 14124 (40.45) 7369 (67.41) 1093 (71.02) <0.001 44 Male, n (%) 22.586 (47.66) 14124 (40.45) 7369 (67.41) 1093 (71.02) <0.001 55 BBI (Mcg/m²) 22.48 ± 2.59 21.25 ± 1.48 25.41 ± 1.05 29.56 ± 1.69 <0.001 58 | $\begin{array}{c c c c c c c c c c c c c c c c c c c $ | | | • | | | | |
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| $ \begin{array}{c c c c c c c c c c c c c c c c c c c $ | $ \begin{array}{c c c c c c c c c c c c c c c c c c c $ | | 511 | doi:10.1016/j.cmet.201 | 7.07.008 | | | |
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| $\begin{array}{c ccccccccccccccccccccccccccccccccccc$ | $\begin{array}{c ccccccccccccccccccccccccccccccccccc$ | | | | ipants, stratified by | Divil gloup | MIIO | <u>מ</u> |
| N473913492010932153943Age (years) 40.95 ± 11.05 40.10 ± 10.70 43.38 ± 11.60 42.93 ± 12.07 <0.001 44Male, n (%) $22586 (47.66)$ $14124 (40.45)$ $7369 (67.41)$ $1093 (71.02)$ <0.001 45BMI (kg/m²) 22.48 ± 2.59 21.25 ± 1.48 25.41 ± 1.05 29.56 ± 1.69 <0.001 47FPG (mmol/L) 4.82 ± 0.52 4.78 ± 0.52 4.92 ± 0.52 4.99 ± 0.54 <0.001 48SBP (mmHg) 110.88 ± 10.24 109.65 ± 10.30 114.07 ± 9.31 116.26 ± 8.63 <0.001 49DBP (mmHg) 69.23 ± 7.47 68.45 ± 7.43 71.22 ± 7.14 72.63 ± 7.13 <0.001 50TG (mmol/L) 0.92 ± 0.34 0.87 ± 0.32 1.06 ± 0.33 1.16 ± 0.32 <0.001 51TC (mmol/L) 1.50 ± 0.26 1.53 ± 0.27 1.42 ± 0.23 1.38 ± 0.21 <0.001 52HDL-C (mmol/L) 2.70 ± 0.62 2.66 ± 0.61 2.80 ± 0.62 2.85 ± 0.63 <0.001 53LDL-C (mmol/L) 20.22 ± 18.34 18.05 ± 16.65 25.39 ± 20.72 32.80 ± 23.65 <0.001 54ALT (mmol/L) 20.22 ± 18.34 18.05 ± 16.65 25.39 ± 20.72 32.80 ± 23.65 <0.001 56AST (mmol/L) 4.63 ± 1.16 4.56 ± 1.14 4.84 ± 1.17 4.91 ± 1.13 <0.001 58SCr (mmol/L) 68.87 ± 15.47 67.05 ± 14.79 73.92 ± 16.32 74.36 ± 14.91 <0.001 <td>42N473913492010932153943Age (years)$40.95 \pm 11.05$$40.10 \pm 10.70$$43.38 \pm 11.60$$42.93 \pm 12.07$$<0.001$44Male, n (%)$22586$ (47.66)14124 (40.45)7369 (67.41)1093 (71.02)$<0.001$45BMI (kg/m²)$22.48 \pm 2.59$$21.25 \pm 1.48$$25.41 \pm 1.05$$29.56 \pm 1.69$$<0.001$46FPG (mmol/L)$4.82 \pm 0.52$$4.78 \pm 0.52$$4.92 \pm 0.52$$4.99 \pm 0.54$$<0.001$48SBP (mmHg)$110.88 \pm 10.24$$109.65 \pm 10.30$$114.07 \pm 9.31$$116.26 \pm 8.63$$<0.001$49DBP (mmHg)$69.23 \pm 7.47$$68.45 \pm 7.43$$71.22 \pm 7.14$$72.63 \pm 7.13$$<0.001$50TG (mmol/L)$0.92 \pm 0.34$$0.87 \pm 0.32$$1.06 \pm 0.33$$1.16 \pm 0.32$$<0.001$51TC (mmol/L)$4.69 \pm 0.80$$4.65 \pm 0.80$$4.79 \pm 0.80$$4.84 \pm 0.79$$<0.001$52HDL-C (mmol/L)$1.50 \pm 0.26$$1.53 \pm 0.27$$1.42 \pm 0.23$$1.38 \pm 0.21$$<0.001$53LDL-C (mmol/L)$2.70 \pm 0.62$$2.66 \pm 0.61$$2.80 \pm 0.62$$2.85 \pm 0.63$$<0.001$54ALT (mmol/L)$20.22 \pm 18.34$$18.05 \pm 16.65$$25.39 \pm 20.72$$32.80 \pm 23.65$$<0.001$56AST (mmol/L)$4.63 \pm 1.16$$4.56 \pm 1.14$$4.84 \pm 1.17$$4.91 \pm 1.13$$<0.001$58SCr (mmol/L)$68.87 \pm 15.47$$67.05 \pm 14.79$$73.92 \pm 16.32$$74.36 \pm 14.91$$<0.001$59<</td> <td></td> <td>variables</td> <td>Total</td> <td></td> <td>MILOW</td> <td>МПО</td> <td></td> | 42N473913492010932153943Age (years) 40.95 ± 11.05 40.10 ± 10.70 43.38 ± 11.60 42.93 ± 12.07 <0.001 44Male, n (%) 22586 (47.66) 14124 (40.45) 7369 (67.41) 1093 (71.02) <0.001 45BMI (kg/m²) 22.48 ± 2.59 21.25 ± 1.48 25.41 ± 1.05 29.56 ± 1.69 <0.001 46FPG (mmol/L) 4.82 ± 0.52 4.78 ± 0.52 4.92 ± 0.52 4.99 ± 0.54 <0.001 48SBP (mmHg) 110.88 ± 10.24 109.65 ± 10.30 114.07 ± 9.31 116.26 ± 8.63 <0.001 49DBP (mmHg) 69.23 ± 7.47 68.45 ± 7.43 71.22 ± 7.14 72.63 ± 7.13 <0.001 50TG (mmol/L) 0.92 ± 0.34 0.87 ± 0.32 1.06 ± 0.33 1.16 ± 0.32 <0.001 51TC (mmol/L) 4.69 ± 0.80 4.65 ± 0.80 4.79 ± 0.80 4.84 ± 0.79 <0.001 52HDL-C (mmol/L) 1.50 ± 0.26 1.53 ± 0.27 1.42 ± 0.23 1.38 ± 0.21 <0.001 53LDL-C (mmol/L) 2.70 ± 0.62 2.66 ± 0.61 2.80 ± 0.62 2.85 ± 0.63 <0.001 54ALT (mmol/L) 20.22 ± 18.34 18.05 ± 16.65 25.39 ± 20.72 32.80 ± 23.65 <0.001 56AST (mmol/L) 4.63 ± 1.16 4.56 ± 1.14 4.84 ± 1.17 4.91 ± 1.13 <0.001 58SCr (mmol/L) 68.87 ± 15.47 67.05 ± 14.79 73.92 ± 16.32 74.36 ± 14.91 <0.001 59< | | variables | Total | | MILOW | МПО | |
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| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$ | $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | | • | 0.92 ± 0.34 | 0.87 ± 0.32 | 1.06 ± 0.33 | 1.16 ± 0.32 | < 0.001 |
| 53InDu C (minor L) 1.50 ± 0.20 1.65 ± 0.27 1.42 ± 0.25 1.50 ± 0.21 40.001 54LDL-C (mmol/L) 2.70 ± 0.62 2.66 ± 0.61 2.80 ± 0.62 2.85 ± 0.63 <0.001 55ALT (mmol/L) 22.49 ± 10.50 21.66 ± 10.15 24.46 ± 10.94 27.46 ± 11.82 <0.001 56AST (mmol/L) 20.22 ± 18.34 18.05 ± 16.65 25.39 ± 20.72 32.80 ± 23.65 <0.001 57BUN (mmol/L) 4.63 ± 1.16 4.56 ± 1.14 4.84 ± 1.17 4.91 ± 1.13 <0.001 58SCr (mmol/L) 68.87 ± 15.47 67.05 ± 14.79 73.92 ± 16.32 74.36 ± 14.91 <0.001 | 53IDD C (Infibilit) 1.50 ± 0.20 1.55 ± 0.27 1.42 ± 0.25 1.50 ± 0.21 <0.001 54LDL-C (mmol/L) 2.70 ± 0.62 2.66 ± 0.61 2.80 ± 0.62 2.85 ± 0.63 <0.001 55ALT (mmol/L) 22.49 ± 10.50 21.66 ± 10.15 24.46 ± 10.94 27.46 ± 11.82 <0.001 56AST (mmol/L) 20.22 ± 18.34 18.05 ± 16.65 25.39 ± 20.72 32.80 ± 23.65 <0.001 57BUN (mmol/L) 4.63 ± 1.16 4.56 ± 1.14 4.84 ± 1.17 4.91 ± 1.13 <0.001 58SCr (mmol/L) 68.87 ± 15.47 67.05 ± 14.79 73.92 ± 16.32 74.36 ± 14.91 <0.001 59Smoking status, n (%) <0.001 <0.001 <0.001 | | TC (mmol/L) | 4.69 ± 0.80 | 4.65 ± 0.80 | 4.79 ± 0.80 | 4.84 ± 0.79 | < 0.001 |
| 54 LDL-C (IIIII0I/L) 2.70 ± 0.62 2.80 ± 0.61 2.80 ± 0.62 2.83 ± 0.63 <0.001 55 ALT (mmol/L) 22.49 ± 10.50 21.66 ± 10.15 24.46 ± 10.94 27.46 ± 11.82 <0.001 56 AST (mmol/L) 20.22 ± 18.34 18.05 ± 16.65 25.39 ± 20.72 32.80 ± 23.65 <0.001 57 BUN (mmol/L) 4.63 ± 1.16 4.56 ± 1.14 4.84 ± 1.17 4.91 ± 1.13 <0.001 58 SCr (mmol/L) 68.87 ± 15.47 67.05 ± 14.79 73.92 ± 16.32 74.36 ± 14.91 <0.001 | 54LDL-C (IIIII0I/L) 2.70 ± 0.62 2.60 ± 0.61 2.80 ± 0.62 2.83 ± 0.63 <0.001 55ALT (mmol/L) 22.49 ± 10.50 21.66 ± 10.15 24.46 ± 10.94 27.46 ± 11.82 <0.001 56AST (mmol/L) 20.22 ± 18.34 18.05 ± 16.65 25.39 ± 20.72 32.80 ± 23.65 <0.001 57BUN (mmol/L) 4.63 ± 1.16 4.56 ± 1.14 4.84 ± 1.17 4.91 ± 1.13 <0.001 58SCr (mmol/L) 68.87 ± 15.47 67.05 ± 14.79 73.92 ± 16.32 74.36 ± 14.91 <0.001 59Smoking status, n (%) <0.001 <0.001 <0.001 | | HDL-C (mmol/L) | 1.50 ± 0.26 | | 1.42 ± 0.23 | 1.38 ± 0.21 | < 0.001 |
| 55ALT (mmol/L) 22.49 ± 10.50 21.66 ± 10.15 24.46 ± 10.94 27.46 ± 11.82 <0.001 56AST (mmol/L) 20.22 ± 18.34 18.05 ± 16.65 25.39 ± 20.72 32.80 ± 23.65 <0.001 57BUN (mmol/L) 4.63 ± 1.16 4.56 ± 1.14 4.84 ± 1.17 4.91 ± 1.13 <0.001 58SCr (mmol/L) 68.87 ± 15.47 67.05 ± 14.79 73.92 ± 16.32 74.36 ± 14.91 <0.001 | 55ALT (mmol/L) 22.49 ± 10.50 21.66 ± 10.15 24.46 ± 10.94 27.46 ± 11.82 <0.001 56AST (mmol/L) 20.22 ± 18.34 18.05 ± 16.65 25.39 ± 20.72 32.80 ± 23.65 <0.001 57BUN (mmol/L) 4.63 ± 1.16 4.56 ± 1.14 4.84 ± 1.17 4.91 ± 1.13 <0.001 58SCr (mmol/L) 68.87 ± 15.47 67.05 ± 14.79 73.92 ± 16.32 74.36 ± 14.91 <0.001 59Smoking status, n (%) <0.001 <0.001 | | · · · · · | | | | | |
| 56AST (mmol/L) 20.22 ± 18.34 18.05 ± 16.65 25.39 ± 20.72 32.80 ± 23.65 <0.001 57BUN (mmol/L) 4.63 ± 1.16 4.56 ± 1.14 4.84 ± 1.17 4.91 ± 1.13 <0.001 58SCr (mmol/L) 68.87 ± 15.47 67.05 ± 14.79 73.92 ± 16.32 74.36 ± 14.91 <0.001 | 56AST (mmol/L) 20.22 ± 18.34 18.05 ± 16.65 25.39 ± 20.72 32.80 ± 23.65 <0.001 57BUN (mmol/L) 4.63 ± 1.16 4.56 ± 1.14 4.84 ± 1.17 4.91 ± 1.13 <0.001 58SCr (mmol/L) 68.87 ± 15.47 67.05 ± 14.79 73.92 ± 16.32 74.36 ± 14.91 <0.001 59Smoking status, n (%) <0.001 <0.001 | | · · · · · · | | | | | |
| 58 SCr (mmol/L) 68.87 ± 15.47 67.05 ± 14.79 73.92 ± 16.32 $74.36 \pm 14.91 < 0.001$ | 58SCr (mmol/L) 68.87 ± 15.47 67.05 ± 14.79 73.92 ± 16.32 74.36 ± 14.91 <0.001 59Smoking status, n (%) <0.001 | 56 | · · · · · · | | | | | |
| | ⁵⁹ Smoking status, n (%) <0.001 | | · · · · · · · · · · · · · · · · · · · | | | | | |
| $50 - 0 - 1^{-1} + 4 - (0/1)$ | | | | | 67.05 ± 14.79 | $7/3.92 \pm 16.32$ | $7/4.36 \pm 14.91$ | |
| $\mathbf{O}_{\mathbf{U}} \mathbf{O}_{\mathbf{U}} \mathbf{O}$ | ~~ | 59 60 | Smoking status, n | (%) | | | | <0.001 |

| 1 | | | | | | 14 |
|----------|----------------------|----------------|--------------|--------------|-------------|---------|
| 2 | | | | | | |
| 3 | Current smoker | 2049 (4.32) | 1277 (3.66) | 667 (6.10) | 105 (6.82) | |
| 4 5 | Ever smoker | 493 (1.04) | 284 (0.81) | 181 (1.66) | 28 (1.82) | |
| 6 | Never smoker | 10221 (21.57) | 7600 (21.76) | 2313 (21.16) | 308 (20.01) | |
| 7 | Drinking status, n (| %) | | | | < 0.001 |
| 8 | Current drinker | 249 (0.53) | 144 (0.41) | 85 (0.78) | 20 (1.30) | |
| 9 | Ever drinker | 2117 (4.47) | 1274 (3.65) | 740 (6.77) | 103 (6.69) | |
| 10 | Never drinker | 10397 (21.94) | 7743 (22.17) | 2336 (21.37) | 318 (20.66) | |
| 11 | Family history of d | iabetes, n (%) | | | | 0.874 |
| 12 13 | Yes | 1061 (2.24) | 789 (2.26) | 239 (2.19) | 33 (2.14) | |

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| | related to text |
| | and data |
| Table 2. Relationship between BMI categories and risk of hyperglycemia among meta healthy participants | ibolically <u>g</u> <u>P</u> |

| | Case/N | Crude Model | Model I | Model II | |
|---------------|------------|-------------------|-------------------|-------------------|---|
| | | (HR, 95% CI) | (HR, 95% CI) | (HR, 95% CI) | |
| Hyperglycemia | | | | | 9 |
| 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

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| | MHNW | MHOW | МНО | <i>P</i> 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) | |
| \geq 40 | 1.00 (Ref.) | 1.22(1.13, 1.31) | 1.53 (1.34, 1.75) | |
| Family history of di | abetes | | | 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) | |
| \geq 170.00 | 1.00 (Ref.) | 1.15 (1.04, 1.26) | 1.50 (1.26, 1.78) | |

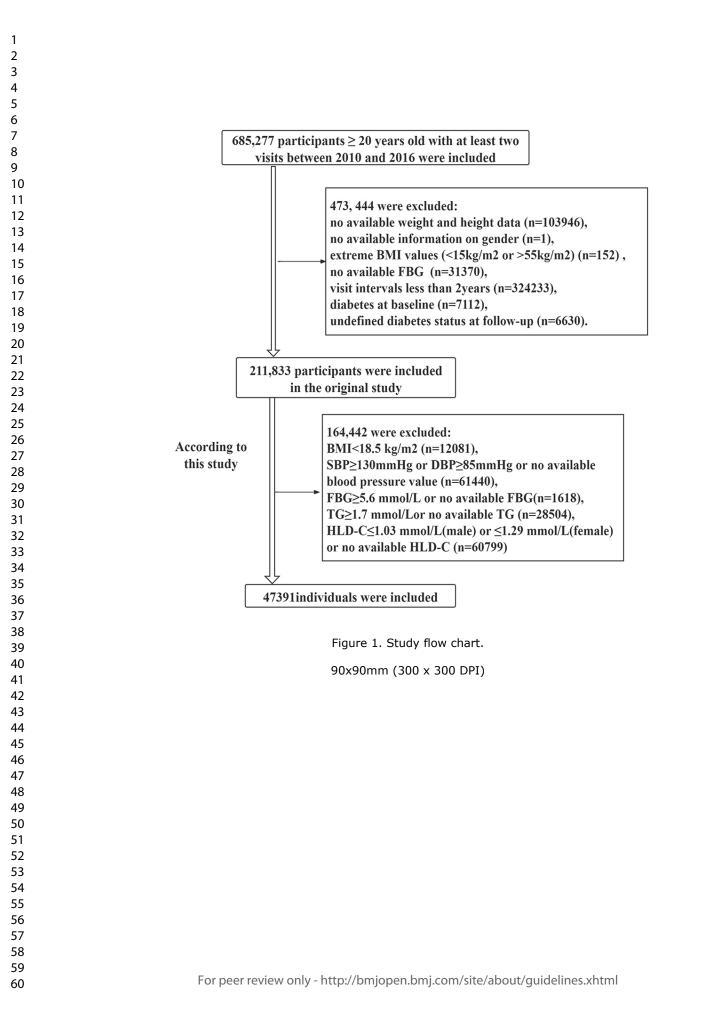
Adjusted for gender (except gender subgroup), age (except age subgroup), family history of diabetes (except "family history of diabetes" subgroup), and baseline FPG, ALT, AST, BUN, SCr, smoking status and drinking status.

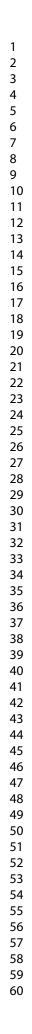
FIGURE LEGENDS

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 BMI, resulting in maximum risk of prediabetes in the MHO group.

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





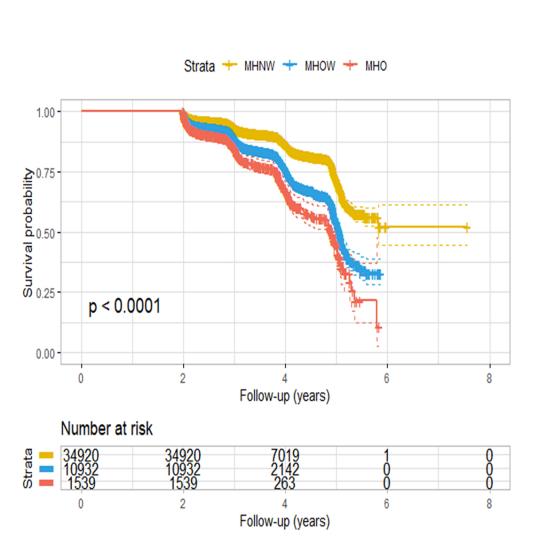


Figure 2. Kaplan–Meier curves for cumulative hazard ratios of incident risk of hyperglycemia. The figure shows that the cumulative risk of incident hyperglycemia was markedly different among the BMI categories (log-rank test, P < 0.001) and increased gradually with increasing BMI, resulting in maximum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

90x90mm (300 x 300 DPI)

| Variables | Non-hyperglycemia | Hyperglycemia | P-value |
|--------------------------|--------------------|-------------------|---------|
| Ν | 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 diabe | etes, n (%) | | 0.039 |
| Yes | 922 (2.19) | 139 (2.64) | |

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The results of univariate analysis for the risk factors of hyperglycemia

| Covariables | HR (95%CI) | <i>P</i> -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

| participants | | | | | |
|--------------|------------|--------------------|-------------------|-------------------|--|
| | Case/N | Crude Model | Model I | Model II | |
| | | (HR, 95% CI) | (HR, 95% CI) | (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) | |
| МНО | 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. |
|--------------------|------------------|-----------------------|--|------------------|
| <i>P</i> for trend | | <0.001 | < 0.001 | < 0.001 |
| - | | and the family histor | y of diabetes; ⁽ , BUN, SCr, smoking | status and drink |
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Table S4

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

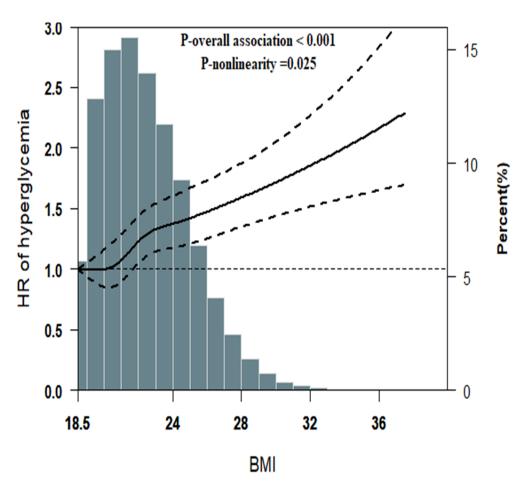
| | Case/N | Crude Model | Model I | Model II |
|-------------|------------|-------------------|-------------------|-------------------|
| | | (HR, 95% CI) | (HR, 95% CI) | (HR, 95% CI) |
| BMI | 1410/12763 | 1.12 (1.10, 1.14) | 1.09 (1.07, 1.11) | 1.05 (1.03, 1.07) |
| MHNW | 844/9161 | 1.00 (Ref.) | 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 |

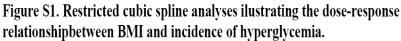
Table S5

| participants wi | ithout missing da | ta of smoking and drink | ing status | | v |
|--------------------|------------------------|---|----------------------------------|-------------------------------|--|
| | Case/N | Crude Model | Model I | Model II | rote |
| | | (HR, 95% CI) | (HR, 95% CI) | (HR, 95% CI) | |
| BMI | 1410/12763 | 1.12 (1.10, 1.14) | 1.09 (1.07, 1.11) | 1.05 (1.03, 1.07) | d by |
| MHNW | 844/9161 | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) | cop |
| MHOW | 485/3161 | 1.73 (1.55, 1.94) | 1.43 (1.27, 1.60) | 1.16 (1.03, 1.30) | yrig |
| MHO | 81/441 | 2.14 (1.70, 2.69) | 1.75 (1.39, 2.21) | 1.28 (1.01, 1.61) | ht, ir |
| P for trend | | <0.001 | < 0.001 | < 0.001 | ncluo |
| 5 | 0 / 0 | r and the family histo seline FPG, ALT, AS | T, BUN, SCr, smoking | status and drinking stat | Protected by copyright, including for uses related to text and data mining, AI training, and similar techn |
| Table S5 | | | | | ıg, ar |
| - | | - | of hyperglycemia among | the metabolically health | hy <mark>si</mark> |
| participants w | vithout missing da | | N 1 1 Y | | nila |
| | Case/N | Crude Model | Model I | Model II | r tec |
| | 2717/10055 | (HR, 95% CI) | (HR, 95% CI) | (HR, 95% CI) | hno |
| BMI | 2717/19955 | 1.14(1.12, 1.15) 1.00(Pof) | 1.11 (1.09, 1.12) 1.00 (Paf) | 1.05(1.04, 1.07) 1.00(Ref) | ologies. |
| MHNW | 1604/14558 945/4742 | 1.00 (Ref.) 1.85 (1.70, 2.01) | 1.00 (Ref.) 1.54 (1.42, 1.67) | 1.00 (Ref.) | es. |
| MHOW | | | 1.54 (1.42, 1.67) | 1.23 (1.13, 1.34) | |
| MHO D for trand | 168/655 | 2.51 (2.15, 2.95) <0.001 | 2.06 (1.75, 2.46) | 1.49 (1.27, 1.76) <0.001 | |
| <i>P</i> for trend | | <u>\0.001</u> | <0.001 | <u>\0.001</u> | |

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

| Model II: status. | further adjuste | ed for baseline FPG | G, ALT, AST, BU | N, SCr, smoking s | tatus and |
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