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# Sex differences in associations of metabolic inflammation and insulin resistance with incident type 2 diabetes mellitus: a retrospective cohort of adults with annual health examinations

Yang Li[1,2†], Xiaotong Guo[1,2†], Jianli Ge[1,2], Qingqing Li[1,2], Xin Chen[1,2], Yingqian Zhu[1,2], Huixiao Yuan[1,2], Shasha Geng[1,2*] and Yue Liu[1,2*]

## Abstract

**Background and aims** Cardio-kidney-metabolic diseases are major causes of premature death worldwide, with type 2 diabetes mellitus (T2DM) playing a critical role. Inflammation and insulin resistance have been implicated in the pathogenesis of T2DM. This study aimed to investigate the sex-specific associations of metabolic inflammation and insulin resistance with incident T2DM to support personalized prevention and management strategies.

**Methods** A retrospective cohort was used to analyse annual health examination data from the general practice department of a general hospital in Shanghai between 2021 and 2023. After excluding participants diagnosed with T2DM, cardiovascular disease or chronic kidney disease at baseline, 1214 adults were followed up for two years. Cox proportional hazards and logistic regression models were used to assess the associations of triglyceride–glucose body mass index (TyG-BMI), the lymphocyte/high-density lipoprotein cholesterol ratio (LHR), the monocyte/high-density lipoprotein cholesterol ratio (MHR), and the neutrophil/high-density lipoprotein cholesterol ratio (NHR) with incident T2DM.

**Results** In the total population, TyG-BMI (all HR/OR > 1, $P < 0.05$), LHR, MHR and NHR were significantly and positively associated with incident T2DM. TyG-BMI was significantly associated with incident T2DM in men (both HR/OR > 1, $P < 0.05$), whereas LHR, MHR and NHR were strongly associated with incident T2DM in women (all HR/OR > 1, $P < 0.05$). The interaction effect between LHR and sex was statistically significant.

**Conclusion** Sex differences play an important role in incident T2DM. Men should be aware of weight control to avoid obesity-related insulin resistance, whereas women should monitor metabolic inflammation indicators such as LHR for early detection and intervention of their T2DM risk.

†Yang Li and Xiaotong Guo contributed equally to this work and share first authorship.

*Correspondence:
Shasha Geng
gengshasha0920@163.com
Yue Liu
liuyue_5_2009@163.com
Full list of author information is available at the end of the article

**Keywords** Type 2 diabetes mellitus, Insulin resistance, Metabolic inflammation, Sex differences, Personalized strategies

## Introduction

The epidemic of cardio-kidney-metabolic (CKM) diseases is a serious global challenge and a leading cause of premature death [1, 2]. Among the major CKM diseases, type 2 diabetes mellitus (T2DM) plays a central role, not only as a result of complex interactions between different types of modifiable and nonmodifiable risk factors early in life but also as a driver of accelerated cardiovascular or renal outcomes [3, 4]. Early prevention of T2DM has been shown to be effective in reducing patients' risk of developing T2DM and in mitigating the downstream effects of the multifaceted CKM syndrome [5–7].

Inflammation and insulin resistance have been recognized as key forces driving the development of CKM syndrome, with equally important implications for the onset and progression of T2DM [8–10]. These processes not only coexist but also act synergistically to amplify metabolic dysfunction, increasing the risk of diabetes and its complications and ultimately leading to cardiovascular or renal death [11–13].

In recent years, there has been an important shift in the measurement of insulin resistance, and many population-validated alternative measures have been developed [14]. Compared with the gold standard, the hyperinsulinaemic-euglycaemic clamp [15], which is difficult to perform and disseminate, the simplest and most feasible alternative is the triglyceride-glucose index (TyG) and its derivatives [16]. Compared with the original TyG index, the triglyceride-glucose body mass index (TyG-BMI) is more strongly associated with the homeostasis model assessment of insulin resistance (HOMA-IR) and is also more predictive of insulin resistance than other TyG derivatives (triglyceride-glucose waist circumference (TyG-WC) and triglyceride-glucose waist height ratio (TyG-WHtR)) [17, 18].

Moreover, interest in novel biomarkers of metabolic inflammation has increased [19], with the ratio of inflammatory cells to high-density lipoprotein cholesterol (HDL-C), including the lymphocyte/high-density lipoprotein cholesterol ratio (LHR), monocyte/high-density lipoprotein cholesterol ratio (MHR), and neutrophil/high-density lipoprotein cholesterol ratio (NHR), considered favourable indicators of inflammation associated with metabolic disorders [20]. Although the relationship between an elevated NHR and adverse cardiovascular outcomes has been demonstrated [21], the relationship between these indicators of metabolic inflammation and incident T2DM remains understudied. Establishing this association will hopefully reveal new pathogenic mechanisms of T2DM and potential targets for therapeutic intervention.

In addition, some studies have shown that there are significant differences in susceptibility to insulin resistance and the inflammatory response between men and women [22–24], suggesting that the development of T2DM may involve different pathophysiological mechanisms in different sexes. Therefore, the effects of sex on indicators of metabolic inflammation and insulin resistance, as well as on the incidence of T2DM, need to be thoroughly investigated.

Based on a retrospective analysis of the population undergoing annual health examinations, this study aimed to assess the associations of metabolic inflammation and insulin resistance with the incidence of T2DM over a two-year follow-up period to explore possible sex differences and, ultimately, to provide additional evidence for personalized prevention and management strategies for cardio-renal metabolic diseases.

## Methods

### Population and study design

This study used annual health examination data from the general practice department of a general hospital in Shanghai between 2021 and 2023. After excluding those with a baseline diagnosis of type 2 diabetes mellitus, cardiovascular disease, or chronic kidney disease ($N=280$), a total of 1,214 adult participants who attended the annual health examination in 2021 and had complete baseline data were followed up for 2 years. The participant screening process and study design framework were shown in Supplementary Fig. 1.

The study adhered to the tenets of the Declaration of Helsinki. As a retrospective cohort study, this study did not involve patient participation or informed consent, and the Ethics Committee of Shanghai East Hospital confirmed that no ethical approval was required.

### Data collection and definition

All the data were obtained from a combination of patients' health records, self-reports, anthropometric measurements and laboratory tests. Demographic information (sex, age) was collected through health records and self-reports, while histories of cardio-kidney-metabolic diseases were assessed through health records, self-reports and laboratory tests. Trained medical staff measured weight and height and calculated BMI. Fasting

blood samples were taken for laboratory tests, including lymphocyte count, neutrophil count, monocyte count, fasting plasma glucose (FPG), glycated haemoglobin (HbA1c), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and serum creatinine.

In this study, we considered 5 categories of cardio-kidney-metabolic disease (hypertension, T2DM, dyslipidaemia, cardiovascular disease, and chronic kidney disease). The relevant definitions and diagnostic criteria were as follows:

Hypertension was defined as previously diagnosed or self-reported hypertension and current antihypertensive treatment; T2DM was defined as previously diagnosed or self-reported type 2 diabetes mellitus, current glucose-lowering therapy, and FPG ≥ 7.0 mmol/L or HbA1c ≥ 6.5% [25]; Dyslipidaemia was defined as previously diagnosed or self-reported dyslipidaemia, current lipid-modifying therapy, and TG ≥ 2.3 mmol/L, TC ≥ 6.2 mmol/L, HDL-C < 1.0 mmol/L, or LDL-C ≥ 4.1 mmol/L [26]; Cardiovascular disease was defined as previously diagnosed or self-reported cardiovascular disease, such as ischaemic heart disease, atrial fibrillation, or heart failure; Chronic kidney disease was defined as previously diagnosed or self-reported chronic kidney disease and an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 $m^2$ based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [27].

#### Metabolic inflammation indicators

We calculated several indicators of metabolic inflammation, including the lymphocyte/HDL-C ratio (LHR), monocyte/HDL-C ratio (MHR) and neutrophil/HDL-C ratio (NHR), based on the blood count and HDL-C level measured in the peripheral blood.

#### Insulin resistance indicators

TyG-BMI was used as an alternative indicator of insulin resistance in this study and was calculated as ln[TG (mg/dl) × FPG (mg/dl)]/2*BMI.

#### Outcome

The outcome (incident T2DM) was defined as a new diagnosis or self-reported T2DM, new use of glucose-lowering therapy, FPG ≥ 7.0 mmol/L or HbA1c ≥ 6.5% at annual health examinations during the 2-year follow-up period.

#### Statistical analyses

The variables were grouped by sex (male/female), and categorical variables were expressed as frequencies and percentages. Differences between groups were tested via the chi-squared test. After testing for normality, continuous variables were expressed as medians (interquartile range) and differences between groups were tested using the Wilcoxon rank-sum test. The log-rank test was used to compare incidence rates (100 person-years) between groups.

Based on prior clinical knowledge, univariate analyses (Supplementary Table 1) and Spearman's rank correlation test (Supplementary Table 2) were performed for statistically significant variables. Sex, age and baseline diagnoses of hypertension and dyslipidaemia were ultimately included as covariates in the adjusted model after variables with correlation coefficients greater than or equal to 0.25 in relation to the TyG-BMI and metabolic inflammation indicators (LHR, MHR and NHR) were excluded. The associations of TyG-BMI, LHR, MHR and NHR with incident T2DM were assessed using Cox proportional hazards models and logistic regression models after conversion of the original TyG-BMI values were divided by 10. Moreover, sex-stratified analysis was performed to test for sex differences in the above associations and possible interactions. In addition, the nonlinear associations of TyG-BMI, LHR, MHR and NHR with incident T2DM were examined via the Cox proportional hazards model and the logistic regression model with restricted cubic splines (RCS).

Participants who are diagnosed with hypertension or dyslipidaemia at baseline may have difficult-to-measure early exposure to metabolic inflammation or insulin resistance. Therefore, we repeated the multivariable-adjusted Cox proportional hazards model and logistic regression model to estimate the associations of metabolic inflammation or insulin resistance with incident T2DM after excluding such participants ($n = 439$). Two other datasets were also considered for sensitivity analyses: (1) excluding participants who did not attend an annual health examination in both 2022 and 2023 ($n = 426$) and (2) excluding participants who were diagnosed with hypertension or dyslipidaemia at baseline or who did not attend an annual health examination in both 2022 and 2023 ($n = 709$). Following the results of the above analyses, the associations of TyG-BMI and LHR with incident T2DM were further examined in the original cohort and the sensitivity analysis cohorts, adjusting for sex, age and baseline diagnoses of hypertension and dyslipidaemia, in the total population, men and women.

All the statistical analyses were performed with STATA 18.0 and R 4.4.1. Hazard ratios (HR) or odds ratios (OR) and 95% confidence intervals were reported, and a two-tailed $P < 0.05$ was considered statistically significant.

**Table 1** Characteristics of the participants at baseline

| | Total (*N* = 1214) | Male (*N* = 678) | Female (*N* = 536) | *P* |
|---|---|---|---|---|
| Female, n(%) | 536(44.15) | - | - | < 0.001 |
| Age(year), [M(IOR)] | 50(40 to 58) | 51(41 to 59) | 48(39 to 56) | < 0.001 |
| BMI(kg/m$^2$), [M(IOR)] | 23.5(21.5 to 25.7) | 24.7(23.2 to 26.8) | 21.7(20.3 to 23.5) | < 0.001 |
| Hypertension, n(%) | 181(14.91) | 137(20.21) | 44(8.21) | < 0.001 |
| Dyslipidaemia, n(%) | 329(27.10) | 230(33.92) | 99(18.47) | < 0.001 |
| SBP(mmHg), [M(IOR)] | 128(118 to 139) | 132(122 to 142) | 123(114 to 134) | < 0.001 |
| DBP(mmHg), [M(IOR)] | 78(71 to 84) | 82(76 to 87) | 73(67 to 79) | < 0.001 |
| FPG(mmol/L), [M(IOR)] | 5.13(4.82 to 5.47) | 5.20(4.88 to 5.58) | 5.07(4.76 to 5.34) | < 0.001 |
| HbA1c(%), [M(IOR)] | 5.5(5.3 to 5.8) | 5.5(5.3 to 5.8) | 5.5(5.0 to 5.6) | < 0.001 |
| TG(mmol/L), [M(IOR)] | 1.17(0.84 to 1.68) | 1.35(0.98 to 1.85) | 1.00(0.74 to 1.42) | < 0.001 |
| TC(mmol/L), [M(IOR)] | 4.79(4.26 to 5.45) | 4.75(4.15 to 5.37) | 4.89(4.33 to 5.52) | 0.002 |
| HDL-C(mmol/L), [M(IOR)] | 1.38(1.15 to 1.67) | 1.23(1.08 to 1.44) | 1.62(1.37 to 1.86) | < 0.001 |
| LDL-C(mmol/L), [M(IOR)] | 3.04(2.55 to 3.56) | 3.08(2.56 to 3.57) | 3.00(2.55 to 3.54) | 0.387 |
| TyG-BMI, [M(IOR)] | 201.24(176.78 to 223.82) | 214.74(196.82 to 235.35) | 179.63(164.69 to 202.19) | < 0.001 |
| LHR, [M(IOR)] | 1.37(1.02 to 1.80) | 1.58(1.20 to 1.98) | 1.13(0.88 to 1.47) | < 0.001 |
| MHR, [M(IOR)] | 0.29(0.21 to 0.39) | 0.35(0.27 to 0.46) | 0.22(0.17 to 0.29) | < 0.001 |
| NHR, [M(IOR)] | 2.21(1.62 to 3.02) | 2.60(1.98 to 3.45) | 1.81(1.36 to 2.47) | < 0.001 |
| Incidence rate(100 person-years) | 3.55 | 3.47 | 3.65 | 0.824 |

*Abbreviations*: *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *TG* triglyceride, *TC* total cholesterol, *HDL-C*, high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TyG-BMI* triglyceride glucose-body mass index, *LHR* lymphocyte-high density lipoprotein cholesterol ratio, *MHR* monocyte-high density lipoprotein cholesterol ratio, *NHR* neutrophil-high density lipoprotein cholesterol ratio

## Results

### Characteristics of the participants at baseline

Among the 1214 participants included in the analysis, 536 (44.5%) were female, with a median age of 50 years, a median BMI of 23.5 kg/m$^2$, and a baseline prevalence of hypertension and dyslipidaemia of 14.91% and 27.10%, respectively. Apart from LDL-C, there were statistically significant differences in baseline characteristics between the male and female subgroups (all $P < 0.05$). Among the female participants, age (48 vs. 51 years), BMI (21.7 kg/m$^2$ vs. 24.7 kg/m$^2$), percentage of hypertension (8.21% vs. 20.21%), percentage of dyslipidaemia (18.47% vs. 33.92%), SBP (123 mmHg vs. 132 mmHg), DBP (73 mmHg vs. 82 mmHg), FPG (5.07 mmol/L vs. 5.20 mmol/L), TG (1. 00 mmol/L vs. 1.35 mmol/L), LDL-C (3.00 mmol/L vs. 3.08 mmol/L), TyG-BMI (179.63 vs. 214.74), LHR (1.13 vs. 1.58), MHR (0.22 vs. 0. 35) and NHR (1.81 vs. 2.60) were greater in men, whereas TC (4.89 mmol/L vs. 4.75 mmol/L) and HDL-C (1.62 mmol/L vs. 1.23 mmol/L) were the opposite. The incidence of T2DM was slightly higher in the female group (3.65/100 person-years) than in the male group (3.47/100 person-years), but the difference was not statistically significant (Table 1).

### Cox proportional hazards model and restricted cubic spline analysis

With TyG-BMI, LHR, MHR and NHR as independent variables, the results of the Cox proportional hazards models were shown as Table 2. The unadjusted model results indicated a positive correlation between the incidence risk of T2DM and TyG-BMI, LHR, MHR and NHR (all $P < 0.05$); after adjustment for sex, age and baseline diagnoses of hypertension and dyslipidaemia, TyG-BMI (HR:1.09, 95% CI:1.02–1.17, $P = 0.013$), LHR (HR:1.47, 95% CI:1.03–2.09, $P = 0.031$), MHR (HR:6.69, 95% CI:1.47–30.52, $P = 0.014$) and NHR (HR:1.25, 95% CI:1.06–1.49, $P = 0.09$) remained significantly associated with the incidence risk of T2DM. Further stratified analysis by sex revealed that TyG-BMI was more strongly associated with the risk of incident T2DM in men ($P = 0.007$), with a slightly higher HR (HR:1.14, 95% CI: 1.04–1.25) than in women (HR:1.11, 95% CI: 1.00–1.23), but the latter was not statistically significant ($P = 0.060$). LHR (HR:2.39, 95% CI:1.39–4.09, $P = 0.002$), MHR (HR:21.18, 95% CI:2.02–221.64, $P = 0.011$) and NHR (HR:1.36, 95% CI:1.08–1.70, $P = 0.008$) were significantly correlated with T2DM incidence risk in women. However, no significant correlation was identified between LHR, NHR and MHR and T2DM incidence risk in men (all $P > 0.05$). Among the interaction terms of sex with TyG-BMI, LHR, MHR and NHR, only the interaction term of sex with LHR was statistically significant ($P$ for interaction were 0.026 and 0.034, respectively), suggesting that sex may influence the association between LHR and incident T2DM.

Using restricted cubic spline analysis, as shown in Fig. 1, no nonlinear relationships were observed between TyG-BMI, LHR, MHR or NHR and the risk of incident

**Table 2** Associations of the TyG-BMI, LHR, MHR and NHR with incident type 2 diabetes mellitus according to Cox proportional hazards models

| | | Crude model | | | Adjusted model[a] | | |
|---|---|---|---|---|---|---|---|
| | | HR(95% CI) | *P* | $P_{interaction}$ | HR(95% CI) | *P* | $P_{interaction}$ |
| TyG-BMI[b] | Total | 1.09(1.02,1.15) | 0.007 | 0.106 | 1.09(1.02,1.17) | 0.013 | 0.193 |
| | Male | 1.16(1.07,1.27) | < 0.001 | | 1.14(1.04,1.25) | 0.007 | |
| | Female | 1.04(0.94,1.16) | 0.440 | | 1.11(1.00,1.23) | 0.060 | |
| LHR | Total | 1.43(1.06,1.92) | 0.019 | 0.026 | 1.47(1.03,2.09) | 0.031 | 0.034 |
| | Male | 1.15(0.75,1.77) | 0.527 | | 1.10(0.68,1.79) | 0.697 | |
| | Female | 2.38(1.47,3.84) | < 0.001 | | 2.39(1.39,4.09) | 0.002 | |
| MHR | Total | 4.68(1.27,17.22) | 0.020 | 0.154 | 6.69(1.47,30.52) | 0.014 | 0.177 |
| | Male | 3.52(0.56,21.96) | 0.178 | | 3.36(0.45,25.03) | 0.237 | |
| | Female | 26.71(3.19,223.68) | 0.002 | | 21.18(2.02,221.64) | 0.011 | |
| NHR | Total | 1.25(1.07,1.45) | 0.005 | 0.302 | 1.25(1.06,1.49) | 0.009 | 0.356 |
| | Male | 1.18(0.95,1.47) | 0.142 | | 1.14(0.90,1.46) | 0.281 | |
| | Female | 1.38(1.13,1.69) | 0.002 | | 1.36(1.08,1.70) | 0.008 | |

*Abbreviations*: *TyG-BMI* triglyceride glucose-body mass index, *LHR* lymphocyte-high density lipoprotein cholesterol ratio, *MHR* monocyte-high density lipoprotein cholesterol ratio, *NHR* neutrophil-high density lipoprotein cholesterol ratio

[a] The adjusted models were adjusted for sex (male as reference), age, and baseline diagnoses of hypertension and dyslipidaemia

[b] TyG-BMI was converted to one-tenth of its original value

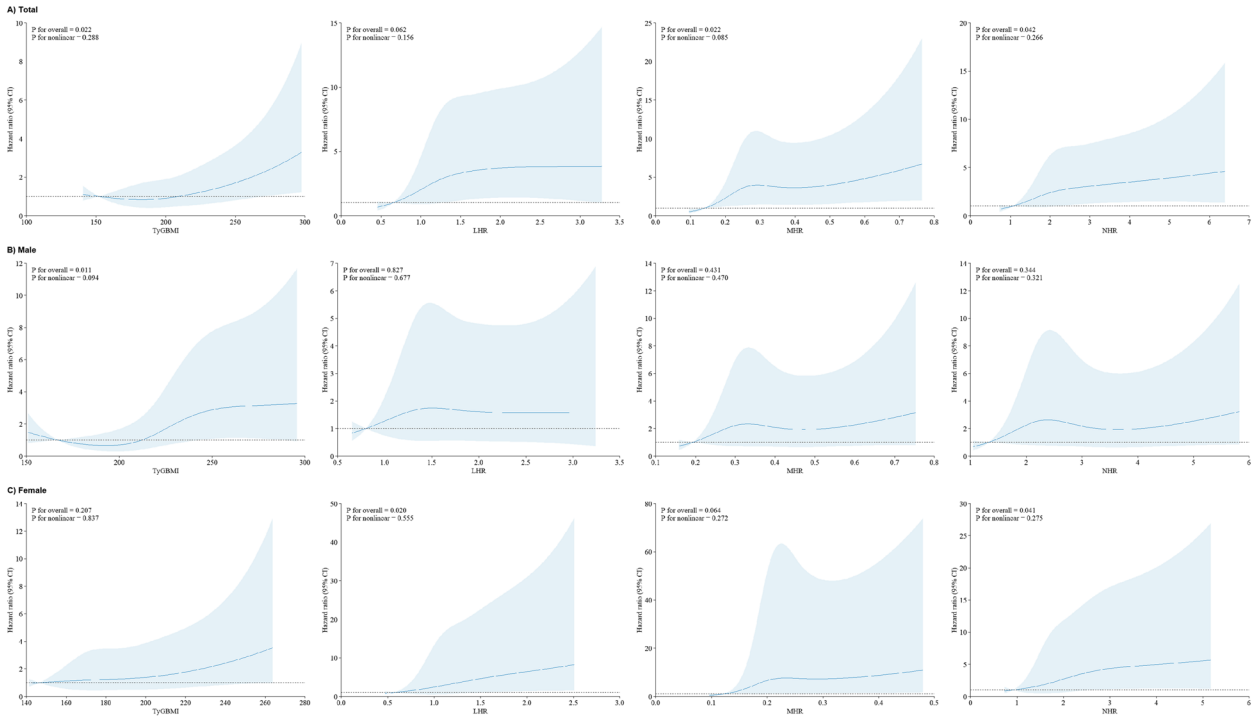


**Fig. 1** Restricted cubic spline curves of TyG-BMI, LHR, MHR and NHR associated with incident type 2 diabetes mellitus according to Cox proportional hazards models in the total population **A**, males **B** and females **C**. All models were adjusted for sex (male as reference), age, and baseline diagnoses of hypertension and dyslipidaemia. Abbreviations: TyG-BMI, triglyceride glucose-body mass index; LHR, lymphocyte-high density lipoprotein cholesterol ratio; MHR, monocyte-high density lipoprotein cholesterol ratio; NHR, neutrophil-high density lipoprotein cholesterol ratio

**Table 3** Associations of the TyG-BMI, LHR, MHR and NHR with incident type 2 diabetes mellitus according to logistic regression models

| | | Crude model | | | Adjusted model[a] | | |
|---|---|---|---|---|---|---|---|
| | | OR(95% CI) | *P* | $P_{interaction}$ | OR(95% CI) | *P* | $P_{interaction}$ |
| TyG-BMI[b] | Total | 1.09(1.03,1.16) | 0.006 | 0.091 | 1.10(1.02,1.18) | 0.010 | 0.164 |
| | Male | 1.18(1.08,1.30) | < 0.001 | | 1.16(1.04,1.29) | 0.006 | |
| | Female | 1.04(0.94,1.16) | 0.424 | | 1.12(1.00,1.25) | 0.053 | |
| LHR | Total | 1.48(1.07,2.03) | 0.016 | 0.021 | 1.52(1.05,2.21) | 0.028 | 0.027 |
| | Male | 1.16(074,1.82) | 0.512 | | 1.10(0.66,1.83) | 0.708 | |
| | Female | 2.70(1.55,4.69) | < 0.001 | | 2.71(1.48,4.98) | 0.001 | |
| MHR | Total | 5.39(1.34,21.60) | 0.017 | 0.129 | 8.13(1.57,41.95) | 0.012 | 0.153 |
| | Male | 3.91(0.57,27.03) | 0.167 | | 3.71(0.44,30.98) | 0.226 | |
| | Female | 47.79(3.59,635.52) | 0.003 | | 36.58(2.33,574.62) | 0.010 | |
| NHR | Total | 1.27(1.08, 1.50) | 0.004 | 0.248 | 1.29(1.07,1.55) | 0.008 | 0.301 |
| | Male | 1.20(0.95,1.52) | 0.129 | | 1.16(0.89,1.49) | 0.268 | |
| | Female | 1.47(1.14,1.88) | 0.002 | | 1.44(1.10,1.89) | 0.008 | |

*Abbreviations*: *TyG-BMI* triglyceride glucose-body mass index, *LHR* lymphocyte-high density lipoprotein cholesterol ratio, *MHR* monocyte-high density lipoprotein cholesterol ratio, *NHR* neutrophil-high density lipoprotein cholesterol ratio

[a] The adjusted models were adjusted for sex (male as reference), age, and baseline diagnoses of hypertension and dyslipidaemia

[b] TyG-BMI was converted to one-tenth of its original value

T2DM (all *P* for nonlinear > 0.05). In the total population, TyG-BMI, MHR and NHR were positively correlated with the risk of incident T2DM (all *P* for overall < 0.05). When stratified by sex, the association between TyG-BMI and incident T2DM was more significant in men (*P* for overall = 0.011), whereas the associations of LHR and NHR with incident T2DM were more significant in women (*P* for overall were 0.020 and 0.041, respectively).

### Logistic regression model and restricted cubic spline analysis

The results of the logistic regression analyses were similar to those of the Cox proportional hazards models (Table 3). TyG-BMI, LHR, MHR and NHR were significantly positively associated with T2DM incidence risk with or without adjustment for sex, age and baseline diagnosis of hypertension and dyslipidaemia (all *P* < 0.05). When stratified by sex, the positive association of TyG-BMI with incident T2DM was more significant in men (OR:1.16, 95% CI:1.04–1.29, *P* = 0.006), and the positive associations of LHR (OR:2.71, 95% CI:1.48–4.98, *P* = 0.001), MHR (OR:36.58, 95% CI:2.33–574.62, *P* = 0.010) and NHR (OR:1.44, 95% CI:1.10–1.89, *P* = 0.008) with incident T2DM were more significant in women. In the interaction analysis, the same statistical significance was observed only for the interaction term of sex and LHR (*P* for interaction were 0.021 and 0.027, respectively).

Additional restricted cubic spline analysis (Fig. 2) failed to detect any nonlinear associations of TyG-BMI, LHR, MHR or NHR with the risk of incident T2DM (all *P* for nonlinear > 0.05). In the total population, TyG-BMI, MHR and NHR were all similarly positively associated with the risk of incident T2DM (all *P* for overall < 0.05). While the association of TyG-BMI with the risk of incident T2DM was more significant in men (*P* for overall = 0.011), the associations of LHR and NHR with the risk of incident T2DM were more significant in women (*P* for overall were 0.019 and 0.040, respectively).

### Sensitivity analyses

After excluding participants with diagnosed hypertension and dyslipidaemia at baseline (Table 4), only LHR was significantly positively associated with the risk of incident T2DM in the total population (HR:1.75, 95% CI:1.02–1.2.99, *P* = 0.042; OR:1.84, 95% CI:1.04–3.26, *P* = 0.037). In terms of sex, the significant positive associations of LHR, MHR and NHR with the risk of incident T2DM in women (all HR/OR > 1, *P* < 0.05) were consistent with the main analysis, and the interaction term between gender and LHR was statistically significant (*P* for interaction were 0.030 and 0.020, respectively).

After excluding participants who did not attend an annual health examination in both 2022 and 2023 (Supplementary Table 3), the correlations between TyG-BMI, MHR and NHR and T2DM incidence risk in the total population (all HR/OR > 1, *P* < 0.05) were similar to the results of main analyses. In the gender stratification, a significant positive relationship between TyG-BMI and the incident T2DM was observed for the first time in

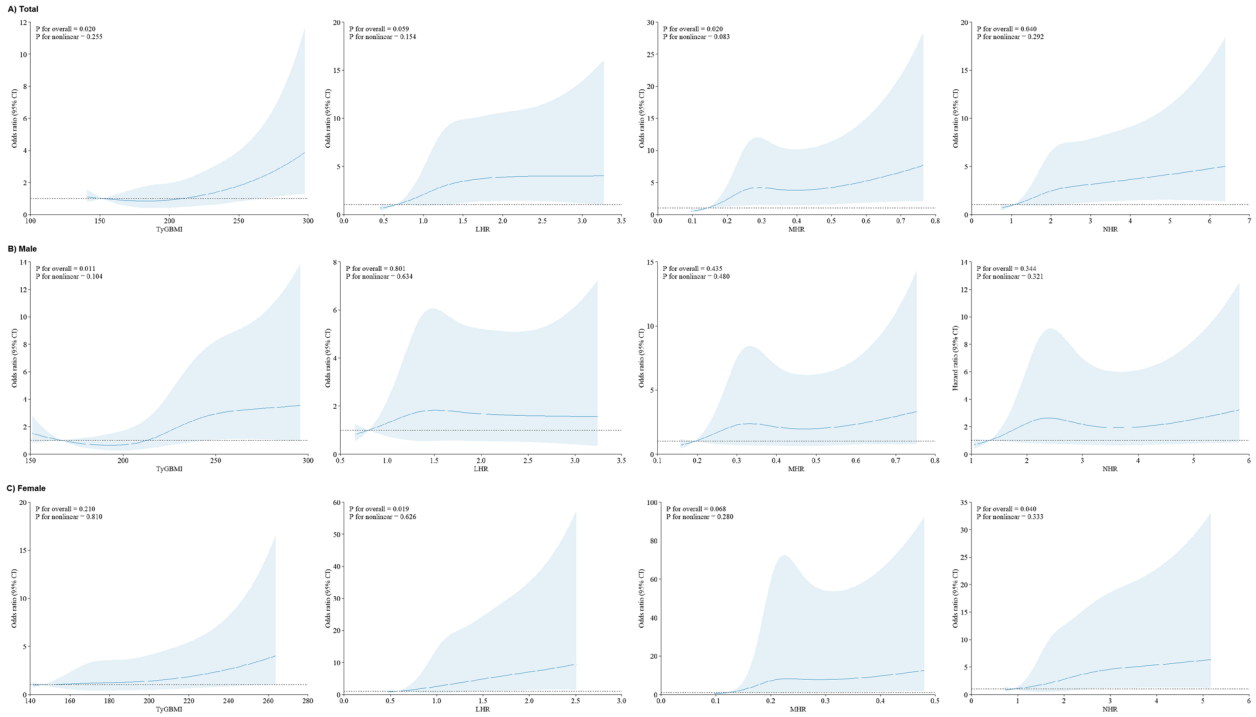


**Fig. 2** Restricted cubic spline curves of TyG-BMI, LHR, MHR and NHR associated with incident type 2 diabetes mellitus according to logistic regression models in the total population **A**, males **B** and females **C**. All models were adjusted for sex (male as reference), age, and baseline diagnoses of hypertension and dyslipidaemia. Abbreviations: TyG-BMI, triglyceride glucose-body mass index; LHR, lymphocyte-high density lipoprotein cholesterol ratio; MHR, monocyte-high density lipoprotein cholesterol ratio; NHR, neutrophil-high density lipoprotein cholesterol ratio

**Table 4** Associations of the TyG-BMI, LHR, MHR and NHR with incident type 2 diabetes mellitus in sensitivity analysis cohort 1 ($N=775$)

| | | Cox proportional hazards model [a] | | | Logistic regression model [a] | | |
|---|---|---|---|---|---|---|---|
| | | **HR(95% CI)** | ***P*** | $P_{interaction}$ | **OR(95% CI)** | ***P*** | $P_{interaction}$ |
| TyG-BMI[b] | Total | 1.07(0.97,1.18) | 0.192 | 0.677 | 1.08(0.97,1.20) | 0.179 | 0.675 |
| | Male | 1.10(0.93,1.29) | 0.261 | | 1.10(0.93,1.30) | 0.248 | |
| | Female | 1.06(0.93,1.21) | 0.382 | | 1.07(0.93,1.23) | 0.363 | |
| LHR | Total | 1.75(1.02,2.99) | 0.042 | 0.030 | 1.84(1.04,3.26) | 0.037 | 0.020 |
| | Male | 0.79(0.30,2.08) | 0.628 | | 0.78(0.29,2.11) | 0.622 | |
| | Female | 2.67(1.41,5.06) | 0.003 | | 3.13(1.51,6.46) | 0.002 | |
| MHR | Total | 6.22(0.68,56.52) | 0.104 | 0.150 | 7.60(0.68,84.69) | 0.099 | 0.124 |
| | Male | 1.20(0.03,48.50) | 0.924 | | 1.21(0.03,55.08) | 0.923 | |
| | Female | 34.50(1.46,814.76) | 0.028 | | 57.10(1.65,1978.95) | 0.025 | |
| NHR | Total | 1.27(0.96,1.68) | 0.088 | 0.038 | 1.31(0.97,1.77) | 0.081 | 0.024 |
| | Male | 0.75(0.41,1.37) | 0.345 | | 0.74(0.40,1.37) | 0.337 | |
| | Female | 1.49(1.12,1.99) | 0.006 | | 1.65(1.15,2.37) | 0.006 | |

*Abbreviations*: *TyG-BMI* triglyceride glucose-body mass index, *LHR* lymphocyte-high density lipoprotein cholesterol ratio, *MHR* monocyte-high density lipoprotein cholesterol ratio, *NHR* neutrophil-high density lipoprotein cholesterol ratio

[a] The adjusted models were adjusted for sex (male as reference) and age

[b] TyG-BMI was converted to one-tenth of its original value

women (HR:1.14, 95% CI:1.02–1.28, $P=0.021$; OR:1.17, 95% CI:1.03–1.33, $P=0.016$) and was slightly greater in women than in men (HR:1.13, 95% CI:1.03–1.24, $P=0.008$; OR:1.16, 95% CI:1.04–1.28, $P=0.006$), but none of the interaction terms between sex and TyG-BMI were statistically significant (both $P$ for interaction > 0.05.). The

significant positive associations of LHR, MHR and NHR with the risk of incident T2DM in women (all HR/OR > 1, $P < 0.05$) were consistent with the main analysis, and the interaction term between sex and the LHR was statistically significant ($P$ for interaction were 0.027 and 0.018, respectively).

After excluding participants who were diagnosed with hypertension or dyslipidaemia at baseline or who did not attend an annual health examination in both 2022 and 2023 (Supplementary Table 4), only LHR and NHR were significantly and positively associated with the risk of incident T2DM in the total population (all HR/OR > 1, $P < 0.05$). Significant positive associations of LHR, MHR and NHR with the risk of incident T2DM in women were still observed in sex stratification (all HR/OR > 1, $P < 0.05$), and the interaction terms of sex with LHR and NHR were statistically significant (all $P$ for interaction < 0.05).

The results of the completely adjusted analyses, including both TyG-BMI and LHR, are shown in Supplementary Table 5. In the total population, TyG-BMI was only significantly associated with incident T2DM when participants who did not attend an annual health examination in both 2022 and 2023 were excluded (both HR/OR > 1, $P < 0.05$). In the male subgroup, the association between TyG-BMI and incident T2DM was statistically significant only when participants with hypertension and dyslipidaemia at baseline were included (both HR/OR > 1, $P < 0.05$). In contrast, in the female subgroup, significant positive associations of LHR with incident T2DM were observed regardless of the cohort datasets (all HR/OR > 1, $P < 0.05$).

## Discussion

This study provides insights into the sex-specific associations of metabolic inflammation and insulin resistance indicators with incident T2DM. The results revealed that (1) TyG-BMI, LHR, MHR and NHR were positively associated with the risk of incident T2DM in the total population and that (2) TyG-BMI was significantly associated with incident T2DM in males, whereas LHR, MHR and NHR were strongly correlated with incident T2DM in females, which may be related to inherent differences in adipose tissue function, metabolic regulation and immune response between males and females [23, 28–31].

Similar to previous findings [32–37], TyG-BMI was significantly associated with the risk of incident T2DM in the primary analyses and was more significant in men, but no interaction between TyG-BMI and sex was ever tested. This finding is also consistent with the sex-specific mechanisms of insulin resistance suggested by previous studies. Men have a greater tendency to develop central obesity, and the chronic low-grade inflammatory state resulting from excess abdominal adiposity activates inflammatory pathways such as nuclear factor kappa-B (NF-κB), which in turn impairs insulin signalling pathways and promotes the onset of insulin resistance [30]. In contrast, although women generally have a greater proportion of subcutaneous adiposity, oestrogens inhibit the production of the inflammatory mediators tumour necrosis factor-α (TNF-α) and interleukin 6 (IL-6), thereby reducing insulin resistance [38]. On the other hand, the effect size (HR/OR) of TyG-BMI failed to maintain robust statistical significance in multiple sensitivity analyses, which may be partly because the follow-up period was short (only 2 years), and some of the participants who were normoglycemic at baseline, even if they had greater insulin resistance, may have just progressed to prediabetes, which is not yet sufficient for the development of T2DM. In addition, compared with the participants included in the sensitivity analyses, those excluded with hypertension and dyslipidaemia at baseline had a relatively higher BMI (24.8 (22.8 to 27.0) kg/m$^2$ vs. 22.8 (21.0 to 24.9) kg/m$^2$) and TyG-BMI (219.45 (199.69 to 242.20) vs. 191.76 (169.62 to 211.82)), which had a significantly higher incidence rate of 4.33/100 person-years vs. 3.11/100 person-years. This could also be a potential explanation for the lack of robustness in the observed effect size for TyG-BMI [39].

The associations of the metabolic inflammation indicators LHR, MHR and NHR with incident T2DM risk were statistically significant overall, especially in the female subgroup, and the significant interaction between LHR and sex was also detected. Compared with previous studies that examined metabolic inflammation indicators and the risk of metabolic syndrome [40–44], this study first investigated their associations with T2DM, a single outcome indicator. In sensitivity analyses, we excluded the effects of hypertension and dyslipidaemia, two important components of metabolic syndrome. In this way, the sex-specific association of T2DM with metabolic inflammation based on adipose dysregulation was assessed quantitatively. A positive association between LHR and T2DM was also found in the baseline analysis of the Prospective Epidemiological Research Studies in Iran (PERSIAN) cohort study and was more significant in women [45]. From a pathophysiological point of view, men tend to have insulin resistance due to excess abdominal adiposity, which is accompanied by a prolonged state of chronic low-grade inflammation [30]. This may cause their LHR to be generally greater than that of women, making it difficult to detect the association between LHR and incident T2DM, even after adjustment for TyG-BMI. While women generally have lower levels of inflammation due to the anti-inflammatory effects of oestrogen, this protective effect may be lost with age and changes in the reproductive cycle, such as a decline

in oestrogen levels after menopause [31]. Furthermore, there are discernible sex-specific differences in the form of prediabetes [46]. The prevalence of impaired glucose tolerance (which reflects postprandial insulin resistance) is greater in women than in men, whereas the prevalence of impaired fasting glucose (which reflects fasting insulin resistance) is greater in men than in women. This may result in a greater proportion of undiagnosed prediabetic women. The risk factors associated with this condition, including psychogenic obesity, insulin resistance, endothelial dysfunction, inflammation, dyslipidaemia and hypertension, are more prevalent and persistent in females than in males [47, 48]. Consequently, there was an even greater sex bias in T2DM management, with females being undertreated [49]. Accordingly, when women are identified with elevated LHR levels, there is potential for undiagnosed prediabetes and an elevated likelihood of developing T2DM. Notably, although the present study did not measure the level of lifestyle exposure, such as smoking, alcohol consumption and physical activity, unhealthy lifestyles may lead to increased levels of inflammation, which may be manifested as an increase in lymphocytes [50]. As a result, the LHR could be considered a composite assessment of the inflammatory state of the organism, integrating metabolic and behavioural correlates [19].

### Strengths and limitations

Notably, this study is the first to evaluate HDL-C-related metabolic inflammation metrics to predict T2DM incidence risk in a Chinese population and provides a new perspective to explore the potential mechanisms of T2DM occurrence by sex through sex-specific association analyses of metabolic inflammation and insulin resistance with incident T2DM. However, this study has several limitations. First, as a single-centre, short-term study, the limited sample size and representativeness limit the ability to extrapolate the findings, and validation in a national cohort is needed. Second, although complex interactions of metabolic factors were considered, TyG-BMI, LHR, MHR and NHR, which are comprehensive measures of the body's inflammatory state and insulin resistance, were included, and several sensitivity analyses were performed. There may still be unmeasured and difficult-to-eliminate confounders. For example, the link between lifestyle and T2DM has been extensively documented, particularly with respect to the effects of alcohol consumption on metabolic processes in the body. However, due to the unavailability of data, this topic could not be discussed. Similarly, serum insulin levels, which are an essential component in calculating HOMA-IR, were not included in the dataset. As a result, it was not possible to assess the precision of the TyG-BMI in quantifying insulin resistance in men and women. Third, because follow-up was performed through annual health examinations, it is difficult to define the time unit (year) of new T2DM diagnosis precisely in months or days, which may slightly overestimate or underestimate the effect value estimated by the Cox proportional hazards model. Finally, only 234 people aged 60 years or older were included in this study, which is less than 20% and not enough to support the model estimation of age stratification. It is necessary to further evaluate the predictive value of LHR for T2DM risk in postmenopausal women through subsequent in-depth studies.

## Conclusion

Overall, according to the present study, TyG-BMI was significantly associated with the risk of incident T2DM in men, whereas increased LHR, MHR and NHR predicted a greater risk of T2DM in women. These findings suggest that sex differences are not only related to biological characteristics but also a nonnegligible factor in the development of CKM diseases, especially T2DM. Recognizing sex differences is essential for developing effective strategies for the prevention and management of T2DM. Men should focus on weight control to avoid central obesity-associated insulin resistance, whereas women should monitor sex-specific indicators of metabolic inflammation, such as LHR, MHR and NHR, to identify and intervene earlier in potential T2DM risk and ultimately reduce the public health costs of comprehensive prevention and treatment of CKM.

## Supplementary Information

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Supplementary Material 1.

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#### Authors' contributions

Yang Li and Xiaotong Guo contributed equally to the study design, data analysis and manuscript drafting. Jianli Ge, Qingqing Li, Xin Chen, Yingqian Zhu, and Huixiao Yuan contributed to the data management and processing. Shasha Geng and Yue Liu were responsible for project supervision and manuscript revision. All authors approved the final version of the manuscript for publication.

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#### Data availability

No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**
The study was conducted via retrospective electronic health records and did not require patient participation or informed consent. The Ethics Committee of Shanghai East Hospital confirmed that no ethical approval was required.

**Competing interests**
The authors declare no competing interests.

**Author details**
[1]Department of General Practice, Shanghai East Hospital, Tongji University School of Medicine, Shanghai 200120, China. [2]Department of Geriatrics, Shanghai East Hospital, Tongji University School of Medicine, Shanghai 200120, China.

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