ONLINE FIRST

ISSN: 0423-104X

e-ISSN: 2299-8306

Non-linear associations of body mass index with impaired fasting glucose, β-cell dysfunction, and insulin resistance in nondiabetic Chinese individuals: a cross-sectional study

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DOI: 10.5603/EP.a2021.0073

Article type: Original paper

Submitted: 2021-03-31

Accepted: 2021-06-30

Published online: 2021-08-06

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Running title: Associations of BMI, FBG, HOMA-β, and IR

10.5603/EP.a2021.0073

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Abstract

Introduction: Identifying and managing patients with prediabetes is important. The study aims to investigate the association of body mass index (BMI) with impaired fasting glucose (IFG), β-cell dysfunction, and insulin resistance in nondiabetic Chinese individuals.

Material and methods: This was a cross-sectional study of consecutive nondiabetic individuals enrolled between January 2014 and January 2015, divided into NFG [normal fasting glucose, fasting blood glucose (FBG) < 5.6 mmol/L) and IFG (n = 450; FBG ≥ 5.6 mmol/L) groups. Restricted cubic splines and piecewise-regression were used to model the association of IFG, impaired β-cell function, and insulin resistance with BMI. Stratified analyses were performed across sex and age.

Results: A total of 900 NFG and 450 IFG individuals were enrolled, with a median

age of 41 (30–49) years and 1076 males (79.7%). After adjusting for age and sex, the restricted cubic splines showed that the risk of IFG was increasing rapidly until around 27.96 kg/m^2 of BMI and then started to plateau afterward (P for non-linearity = 0.010), which was similar in males and individuals ≤45 years old (P for non-linearity < 0.001 and = 0.007, respectively). The risk of insulin resistance increased and β-cell dysfunction decreased as the BMI increased in all participants (both P for non-linearity > 0.05), consistent with the results in males, females, and ≤ 45 and > 45 year olds.
Conclusions: The risk of IFG does not rise linearly as the BMI increases, and higher BMI seems to decelerate the rise of the risk.
Key words: insulin-secreting cells; insulin resistance; blood glucose; body mass index

Introduction

The prevalence of diabetes in Chinese adults has been increasing rapidly since 2000, with an annual growth rate of 0.72% (95% CI: 0.34–1.10%) [1]. In a nationally representative cross-sectional survey carried out in 2013, the estimated overall prevalence of diabetes among adults in China was 10.9%, and that for prediabetes was 35.7% [2]. Once developed, type 2 diabetes (T2DM) is an irreversible condition [3]. Individuals with prediabetes will eventually progress to overt diabetes, but it can be delayed with the appropriate changes in lifestyle habits and with drugs when necessary. Individuals with prediabetes will have no signs or symptoms but will show impaired fasting glucose (IFG). Identifying and managing patients with prediabetes is important because chronic hyperglycaemia of diabetes can lead to multiorgan damage resulting in renal, neurological, cardiovascular, and other serious complications [3] and is associated with significant morbidity and mortality [4].

The major underlying pathophysiology of T2DM in the Chinese population is the same as in other populations, i.e. β-cell dysfunction and insulin resistance [5]. Insulin resistance is defined as an impaired peripheral sensitivity to normal or elevated insulin levels. Compensatory hyperinsulinaemia occurs when insulin secretion increases to maintain blood glucose levels at normal levels. Hence, high fasting insulin (FINS) levels may indicate insulin resistance [6]. The abnormal function of pancreatic islet β-cells is characterized by impairments ranging from impaired insulin pulse secretion to the lack of insulin secretion in the first phase and increased compensation in the second phase [7]. In the decompensated stage, both the 1- and 2-phase secretions are decreased. In the United Kingdom Prospective Diabetes Study (UKPDS), the β-cell

function was lower by about 50% when fasting hyperglycaemia was diagnosed [8].

High adiposity, as reflected by a high body mass index (BMI), is the most important independent risk factor for T2DM [9]. Homeostasis model assessment (HOMA) equations are tools used to estimate insulin resistance. HOMA-IR is used to assess insulin resistance, while HOMA-β is used to assess pancreatic β-cell function [10]. A study in Caucasians showed that the HOMA-IR is dependent upon sex, age, and BMI categories, with obese people having high HOMA-IR [11]. Both β-cell dysfunction and insulin resistance contribute to high levels of fasting blood glucose (FBG) and the progressive deterioration from impaired glucose regulation (IGR) to T2DM; when IGR signs start to manifest, FBG may still be in the normal range [12]. The degree of β-cell dysfunction is a determinant for the FBG levels, with decreased insulin secretion by β-cells and peripheral insulin resistance contributing to increased FBG levels [13]. In subjects with T2DM, β-cell secretory capacity is reduced by approximately 75% when the FBG levels increase [14]. Previous studies have suggested that deterioration of basal and early-phase insulin secretion, rather than insulin sensitivity, is crucial to the progression from normal glucose tolerance (NGT) to T2DM [15].

Nevertheless, there is a lack of data about the relationship between FBG and β-cell function during the progression from NFG to IFG according to the different BMI levels. Therefore, this study aimed to investigate the association of BMI with IFG, β-cell dysfunction, and insulin resistance in nondiabetic Chinese individuals. The results could help identify the individuals at higher risk of progression to T2DM in whom early lifestyle changes should be undertaken.

Material and methods

Study design and participants

This cross-sectional study enrolled consecutive nondiabetic individuals from the Physical Examination Centre of our Hospital from January 2014 to January 2015. This study was approved by the Ethics Committee of our Hospital. All participants provided written informed consent.

The inclusion criteria were as follows: 1) 18–80 years of age; 2) no medical history of heart disease, brain disease, lung disease, high blood pressure (systolic blood pressure [SBP] ≥ 140 mmHg and/or diastolic blood pressure [DBP] ≥ 90 mmHg measured 3 times on different days, without medication), blood lipid disorders (total cholesterol [TC] ≥ 5.2 mmol/L, low-density lipoprotein cholesterol [LDL-C] ≥ 3.4 mmol/L, triglyceride [TG] ≥ 1.7 mmol/L, or high-density lipoprotein cholesterol

[HDL-C] < 1.0 mmol/L, without medication), chronic hepatitis (viral hepatitis, autoimmune liver disease, drug-induced liver disease, liver cancer and cirrhosis, and no history of medication), and chronic kidney disease (chronic glomerulopathy, renal tubular disease, interstitial nephritis, and renal vascular disease, and the serum creatinine is normal), and 3) markers of liver and kidney functions were all within the normal range. The exclusion criteria were 1) FBG ≥ 7.0 mmol/L or glycated hemoglobin (HbA_{1c}) ≥ 6.5%, 2) use of anti-hypertension drugs, anti-dyslipidemia drugs, or any medications known to affect insulin sensitivity within the past 6 months, including weight-loss drugs, Chinese herbal medicines, anti-diabetic drugs, and insulin; 3) severe organ dysfunction or mental illness; or 4) history of diabetes mellitus, severe anaemia, pancreatitis, acute myocardial infarction, or stroke.

Grouping

According to the diagnostic criteria for IFG by the American Diabetes Association (ADA) in the United States [16], the individuals were divided into 2 groups based on FBG: IFG (FBG ≥ 5.6 mmol/L) and NFG (FBG < 5.6 mmol/L).

Data collection and definitions

Basic demographic data (i.e. age, sex, body height, and weight) were collected. Height and weight were measured to the nearest 0.1 cm and 0.1 kg by the same well-trained examiner. Body mass index (BMI) was calculated as follows:

$$body\ weight\ (kg)/[height\ (m)]^2.$$

Fasting (overnight) serum samples were collected from a peripheral vein. Serum samples were stored at –80°C. TC, HDL-C, LDL-C, and TG levels were measured by colorimetric enzymatic assays using a 7170 autoanalyzer (Hitachi, Tokyo, Japan). Reference intervals for TC, HDL-C, LDL-C, and TG were 3.62–5.70 mmol/L, 1.03–1.55 mmol/L, 1.81–3.36 mmol/L, and 0.56–1.70 mmol/L, respectively [17]. HbA1c was measured using a Variant II HbA1c analyser (Bio-Rad Laboratories, Hercules, CA, USA). Alanine aminotransferase (ALT), aspartate aminotransferase (AST), FBG, HbA1c, and FINS levels were measured routinely at the central biochemistry laboratory of our hospital.

The HOMA-IR and HOMA-β were determined. HOMA-IR was calculated according to the following formula:

$$HOMA\text{-}IR = [FBG\ (mmol/L) \times FINS\ (\mu IU/mL)]/22.5,$$

And HOMA-β was calculated as follows:

$$HOMA\text{-}\beta = [20\times FINS\ (\mu IU/mL)]/[FBG\ (mmol/L)–3.5].$$

Insulin resistance was defined as higher than the 75th percentile of HOMA-IR in participants with a normal BMI and normal fasting glucose [18], which was 2.726 in

this study. Impaired β-cell function was defined as lower than the 25th percentile of the HOMA-β in participants with a normal BMI and normal fasting glucose [12, 18], which was 73.988 in this study.

Statistical analysis

Continuous data were presented as mean ± standard deviation or median (upper and lower quartiles) and analysed using Student's t-test. Categorical variables are presented as frequencies and were analysed using the chi-square test. The significance of the mean differences for the indexes of insulin resistance and β-cell function (HOMA-IR, HOMA-β, and FINS) was tested using general linear models after adjustment for age, sex, and BMI. The associations between insulin resistance, β-cell dysfunction, and IFG with BMI were evaluated by restricted cubic spline regression, adjusting for age and sex**. The number of dots was chosen to 4 knots at the 5th, 35th, 65th, and 95th centiles.** Piecewise-regression models were then performed to quantify associations: where there was evidence of non-linearity, a piecewise-regression model with a single change point was estimated by trying all possible values for the change point and choosing the value with the highest likelihood. Moreover, stratified analyses were performed to explore whether the association varied across sex and age. Data analysis was performed using SPSS 22.0 (IBM, Armonk, NY, USA) and R 4.0.2 (The R Project for Statistical Computing, www.r-project.org). GraphPad Prism 8 (GraphPad Software Inc., San Diego, CA, USA) was used to draw the figures. All tests were two-tailed, and p values < 0.05 were considered statistically significant.

Results

Characteristics of the participants

A total of 1350 participants, including 900 individuals in the NFG group and 450 in the IFG group, were enrolled from the Physical Examination Centre of our Hospital between January 2014 and January 2015 and analysed. The mean age was 41 (30–49) years and most participants were male (79.6%) (Tab. 1). There were significant differences in age, BMI, and blood pressure between the two groups (all $p < 0.05$).

In addition, higher levels of TC, TG, and LDL-C and lower levels of HDL-C were observed in the IFG group (all $p < 0.05$). Compared with the NFG group, FINS and HOMA-IR were significantly higher in the IFG group (FINS: 12.75 ± 0.24 vs. 15.35 ± 0.34; HOMA-IR: 2.97 ± 0.06 vs. 4.09 ± 0.09), while HOMA-β was lower (150.1 ± 2.4 vs. 125.6±3.5) (all $p < 0.05$).

Association of IFG, impaired β-cell function, and insulin resistance with BMI

After adjusting for age and sex, restricted cubic spline regression showed that the risk of insulin resistance increased rapidly as the BMI increased, and the non-linearity was not significant ($p = 0.725$, Fig. 1A), indicating that the risk of insulin resistance increased as BMI increased, or, in some way, high BMI was a risk factor of insulin resistance. In contrast, the risk of β-cell dysfunction decreased in an approximately linear fashion (p for non-linearity = 0.851, Fig. 1B), meaning that the risk of β-cell dysfunction decreased as BMI increased, or, in some way, high BMI was a protective factor of β-cell function. Notably, the risk of IFG increased rapidly until around 27.96 kg/m^2 of BMI and then started to plateau afterward (p for non-linearity = 0.010, Fig. 1C), indicating that the risk of IFG increased as the BMI increased, but higher BMI seemed to decelerate the increase of the risk.

Association of IFG, impaired β-cell function, and insulin resistance with BMI by age

After stratifying all participants into the 18–45- and > 45-year-old subgroups, younger individuals showed a lower prevalence of IFG and β-cell dysfunction (both $p < 0.001$, Fig. 2A). Meanwhile, no significant difference was found regarding the prevalence of insulin resistance. Restricted cubic spline regression showed that the risk of insulin resistance increased and β-cell dysfunction decreased as BMI increased, and the non-linearity was not significant whether in younger or older individuals (all p for non-linearity > 0.05, Fig. 3A, B, D, and E). Consistent with asll of the individuals, the risk of IFG increased rapidly until around 27.51 kg/m^2 of BMI and then started to plateau afterward in 18–45-year-old individuals (p for non-linearity = 0.007, Fig. 3C). On the other hand, the non-linearity seemed to disappear in older individuals (p for non-linearity = 0.212, Fig. 3E). The results suggest that in younger individuals, the risk of IFG increased as the BMI increased, but higher BMI seemed to decelerate the increase of the risk, while still being linked to increased risk in older individuals.

Association of IFG, impaired β-cell function, and insulin resistance with BMI by sex

Stratified analysis showed that male individuals had a higher prevalence of IFG and insulin resistance (both $p < 0.001$, Fig. 2B). Meanwhile, no significant difference was found regarding the prevalence of β-cell dysfunction. Restricted cubic spline regression showed that the risk of insulin resistance increased and impaired β-cell function decreased as BMI increased, and the non-linearity was not significant

whether in male or female individuals (all p for non-linearity > 0.05, Fig. 4A, B, D, and E). As with all the individuals, the risk of IFG increased rapidly until around 24.26 kg/m^2 of BMI and then started to plateau afterward in male individuals (P for non-linearity < 0.001, Fig. 4C). However, the non-linearity seemed to disappear in female individuals (p for non-linearity = 0.349, Fig. 4E). Hence, in males, the risk of IFG increased as the BMI increased, but higher BMI seemed to decelerate the increase of the risk, while high BMI still increased the risk in females.

Discussion

This study aimed to investigate the association of BMI with IFG, β-cell dysfunction, and insulin resistance in nondiabetic Chinese individuals. The results show that the risk of IFG is not rising linearly as the BMI increases, and higher BMI seems to decelerate the rise of the risk. The findings suggest that the compensated secretion of β cells might play a valuable role against insulin resistance in high-BMI individuals.

Overweight or obesity is a major risk factor for prediabetes and T2DM. In Northeast China, the prevalence of overweight is 42%, the prevalence of obesity is 20.1%, and the prevalence of central obesity is 58.9% in adults with prediabetes [19]. Abdominal obesity accounts for 28.1% of incident cases of diabetes among men and 41.2% among women [20]. FINS and HOMA-IR were higher in the IFG group than in the NFG group, while HOMA-β was lower in the IFG group. It is consistent with the concept of progressive insulin resistance and β-cell dysfunction from NFG to T2DM [14]. High FBG is one of the main characteristics of T2DM. In the postprandial state, T2DM defined by HbA1c levels was associated with both α- and β-cell dysfunction and impaired insulin response combined with non-suppressed glucagon [21]. In the fasting state, the liver maintains blood glucose levels for the brain’s need for glucose. Thus, insulin resistance of the liver plays a key role in high FBG levels. IFG is an intermediate status between NFG and T2DM, and the present study showed that HOMA-IR increased from NFG to IFG, which is supported by the literature [11, 22].

In addition to insulin resistance, β-cell dysfunction is well recognized as central to the pathophysiology of prediabetes and diabetes. The earliest detectable abnormality in individuals at risk of T2DM is insulin hypersecretion, which aims to compensate for insulin resistance in peripheral tissues. Nevertheless, T2DM does not occur until the β-cells become unable to secrete enough insulin to overcome

peripheral insulin resistance. In some Chinese analyses evaluating the role of β-cell function in increasing FBG, the disposition index, a value representing β-cell function, was decreased by 38% in IFG [12], and HOMA-β progressively declined by 33% in IFG and reached a substantial decrease of 41% in the diabetic range of FBG [23]. Previous studies suggested that the deterioration of basal and early-phase insulin secretion, rather than insulin sensitivity, is crucial to the progression from NGT to T2DM [15]. Sun et al. [24] found that in overweight Chinese adolescents with normal glucose tolerance, insulin resistance progressively increased with increasing BMI, but the compensatory increase in early insulin secretion was limited. Roth et al. [25]. found that the OGTT 30-min/120-min insulin ratio was significantly lower in obese children, which indicated that these children already had inadequate β-cell compensation for the degree of insulin resistance [25]. In the present study, the cubic spline analyses showed that the risk of insulin resistance increased as the BMI increased, meaning that high BMI was a risk factor of insulin resistance. In addition, the risk of impaired β-cell function decreased as the BMI increased, suggesting that high BMI was a protective factor of impaired β-cell function. The compensated secretion of β cells might contribute to the phenomenon.

Interestingly, different relationships were observed between younger and older individuals and between males and females. The differences of IFG and β-cell function in younger and older individuals revealed that the main cause of the higher prevalence of IFG in older individuals might be worse β-cell function. The disappearance of non-linearity in older individuals might be due to a worse β-cell function and worse compensated secretion function of β-cells. It is consistent with the literature showing that β-cell function decreases with age [26, 27]. The differences of IFG and insulin resistance in male and female individuals revealed that the main cause of the higher prevalence of IFG in male individuals might be insulin resistance. In addition, the change point of BMI **was lower in males than in whole individuals**. Because of the high prevalence of insulin resistance in men, compensatory insulin secretion might be more common in men [28]. Sex hormones play a role in developing insulin resistance and T2DM [28, 29].

It is now recognized that β-cell failure occurs much earlier and is more severe than previously thought [30]. Individuals with FBG in the upper range have decreased β-cell function and decreased insulin sensitivity before the onset of diabetes, and Asians are more likely to have lower β-cell mass and insulin secretory capacity

compared with Caucasians [31], suggesting that a small decline in β-cell function could be enough to precipitate progression to overt T2DM in Asians. A study of 1835 Japanese patients demonstrated that insulin secretory defect and decreased insulin sensitivity were found in patients with IFG in the range 5.6–6.1 [32]. The present study showed that insulin resistance and β-cell dysfunction were deteriorated when FBG was ≥ 5.6 mmol/L. It may suggest that the optimal time to intervene is before the FBG is ≥ 5.6 mmol/L in the Chinese population, to prevent the progression of T2DM and its complications. It is supported by a previous study that showed distinct lipid patterns across FBG levels in different ethnicities [33].

The present study has some limitations. Firstly, we used the HOMA-β to evaluate pancreatic β-cell function. HOMA-β is not a precise index compared to the hyperglycaemic clamp, but the clamp is expensive and time-consuming, and it is difficult to carry out in the setting of a large-scale epidemiological study. Secondly, we did not take into account the level of physical activity of the participants, which might significantly affect FBG, insulin concentration, and insulin resistance. Finally, males outnumbered females in this study because the population were enrolled at the hospital's medical examination centre. Most participants were men with good economic conditions, which resulted in a limited analysis of female individuals. Further studies are necessary to address this issue.

Conclusion

The risk of IFG does not rise linearly as the BMI increases, and higher BMI seems to decelerate the rise of the risk. The association of BMI with the risk of IFG decelerates at high BMI values in younger individuals and males. The findings suggest that the compensated secretion of β cells might play a valuable role against insulin resistance in high-BMI individuals. These results could help identify individuals at higher risk of progression to T2DM in whom early lifestyle changes should be undertaken, and it could contribute personalized management.

Conflict of interest

All the authors declare no conflict of interests.

Funding

The authors acknowledge the help of the National Natural Science Foundation of China (No. 81770792).

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Table 1. Characteristics of the subjects

Characteristics	**Total (n = 1350)**	**NFG (n = 900)**	**IFG (n = 450)**	**p**
Age [years]	41 (30, 49)	37 (29, 47)	45 (37, 52)	< 0.001
Males [n (%)]	1076 (79.7)	682 (75.8)	394 (87.6)	< 0.001
BMI [kg/m^2]	24.8 (22.3, 27.0)	24.3 (21.7, 26.7)	25.8 (23.9, 27.7)	< 0.001
SBP [mmHg]	123 (114, 133)	121 (112, 130)	127 (118, 136)	< 0.001
DBP [mmHg]	74 (68, 82)	73 (67, 80)	79 (72, 86)	< 0.001
ALT [U/L]	23 (16, 34)	21 (16, 32)	26 (19, 37)	< 0.001
AST [U/L]	20 (17, 24)	19 (16, 23)	21 (18, 25)	< 0.001
TG [mmol/L]	1.25 (0.83, 1.93)	1.12 (0.77, 1.77)	1.51 (0.98, 2.26)	< 0.001
TC [mmol/L]	4.89 (4.33, 5.54)	4.81 (4.22, 5.43)	5.07 (4.55, 5.74)	< 0.001
HDL-C [mmol/L]	1.19 (1.03, 1.41)	1.21 (1.04, 1.44)	1.15 (1.00, 1.35)	< 0.001
LDL-C [mmol/L]	2.83 (2.38, 3.36)	2.76 (2.32, 3.33)	2.94 (2.55, 3.39)	< 0.001
FBG [mmol/L]	5.40	5.23 (5.03, 5.40)	5.88 (5.71, 6.15)	< 0.001

	(5.13, 5.71)			
HBA_{1c} (%)	5.7 (5.5, 5.9)	5.5 (5.4, 5.7)	5.8 (5.6, 6.0)	< 0.001
FINS [mU/L]	11.71 (8.08, 16.60)	10.67 (7.38, 15.46)	13.41 (9.72, 18.72)	< 0.001
FINS [mU/L][a]	14.05 ± 0.20	12.75 ± 0.24	15.35 ± 0.34	< 0.001
HOMA-IR	2.86 (1.90, 4.07)	2.51 (1.69, 3.63)	3.55 (2.62, 4.97)	< 0.001
HOMA-IR[a]	3.53 ± 0.05	2.97 ± 0.06	4.09 ± 0.09	< 0.001
HOMA-β	120.0 (84.5, 172.6)	126.5 (88.0, 181.2)	111.5 (78.2, 156.1)	< 0.001
HOMA-β[a]	137.9 ± 2.1	150.1 ± 2.4	125.6 ± 3.5	< 0.001

Normally distributed variables are expressed as mean ± standard deviation (SD), while variables with skewed distribution (age, ALT, AST, TG, FINS, HOMA-IR, and HOMA-β are expressed as medians [upper and lower quartiles]). BMI: — body mass index; SBP: — systolic blood pressure; DBP: — diastolic blood pressure; ALT: — alanine aminotransferase; AST: — aspartate aminotransferase; TC: — total cholesterol; TG: — triglyceride; HDL-C: — high-density lipoprotein cholesterol; LDL-C: — low-density lipoprotein cholesterol; FBG: — fasting blood glucose; FINS: — fasting insulin; HOMA-IR: — homeostasis model assessment of insulin resistance; HOMA-β: — homeostasis model assessment of β-cell function; [a]adjusted for age, sex, and BMI

Figure 1. Association between body mass index and insulin resistance (**A**), β-cell dysfunction (**B**), and impaired fasting glucose (IFG) (**C**)

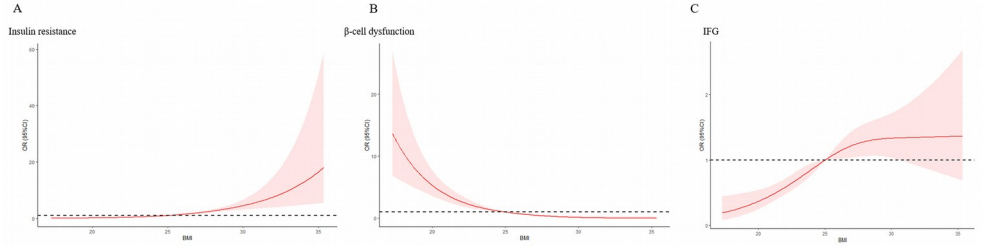

Figure 2. Prevalence of impaired fasting glucose (IFG), β-cell dysfunction, and

insulin resistance among nondiabetic patients by age (**A**) and sex (**B**). ***represented $p < 0.001$

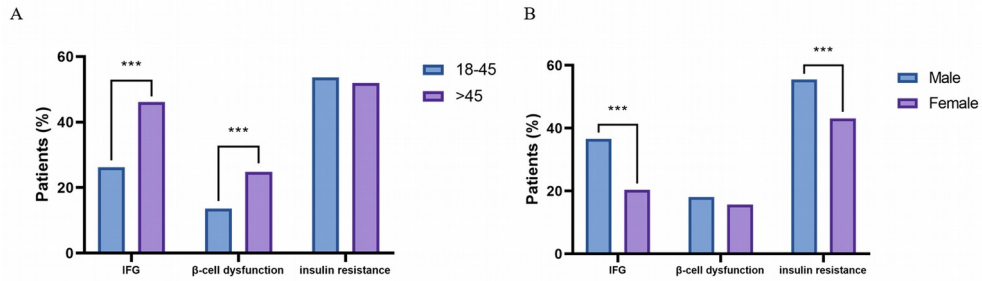

Figure 3. Association between body mass index and insulin resistance (**A**, **D**), β-cell dysfunction (**B**, **E**), and impaired fasting glucose (IFG) (**C**, **F**) in nondiabetic 18–45- (**A–C**) and > 45-year-old (**D–E**) individuals

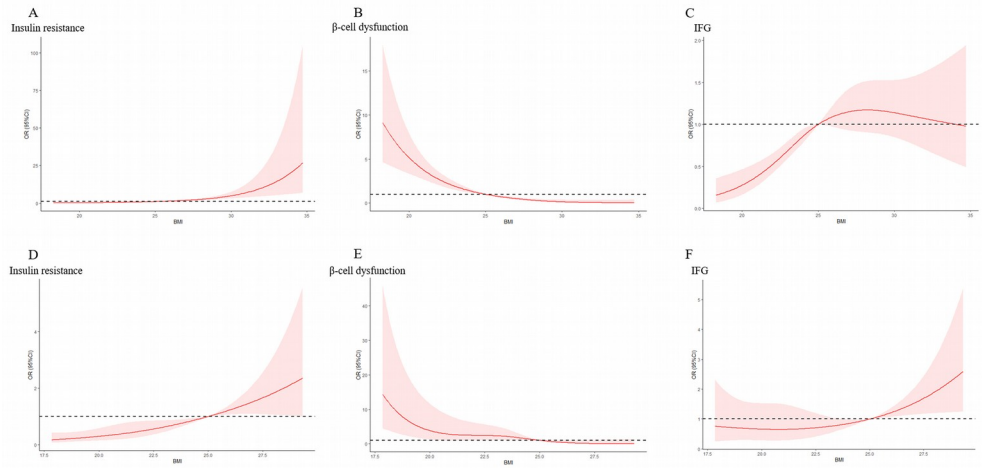

Figure 4. Association between body mass index and insulin resistance (**A, D**), β-cell dysfunction (**B, E**), and impaired fasting glucose (IFG) (**C, F**) in nondiabetic male (**A–C**) and female (**D–E**) individuals