Sex Differences in the Nonlinear Association Between BMI and LDL Cholesterol in Middle-Aged and Older Adults: Results from two Nationally Representative Surveys of China

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Abstract

Background: The association between body mass index (BMI) and low-density lipoprotein cholesterol (LDL-C) in middle-aged and older man and women was understudied. We aimed to explore whether there were sex differences in this relationship in a large sample of Chinese adults.

Methods: Participants in the China Health and Retirement Longitudinal Study (CHARLS, 2011-2012) (n=7485) and the China Health and Nutrition Survey (CHNS, 2009) (n=4788) were cross-sectionally investigated. Generalized additive models with a smooth function for BMI and a smooth-factor interaction for BMI with sex were performed and stratified by age and metabolic syndrome. Segment linear splines regressions were fitted to calculate the slopes with the different breakpoints.

Results: Among the 12273 participants aged 45 to 75 years, 5780 (47.1%) were males. The nonlinear relationship between BMI and LDL-C was observed in females and males ($P_{\text{interaction}} < 0.001$). The slopes of the BMI and LDL-C association changed ($P < 0.001$) at BMI 22.5 kg/m² in females and 27.5 kg/m² in males. Below these BMI breakpoints, LDL-C increased 2.14 (95% CI: 1.42 to 2.86) and 1.77 (95% CI: 1.43 to 2.11) mg/dL per kg/m², respectively. In females, there was a plateau at BMI values of 22.5-27.5 kg/m², and then gradually increased after a BMI of 27.5 kg/m². However, LDL-C declined -1.84 (95% CI: -3.01 to -0.66) mg/dL per kg/m² above BMI of 27.5 kg/m² in males. The pattern of sex and BMI-LDL-C association was similar in all age groups but modified by the number of metabolic syndrome criteria.

Conclusions: The BMI and LDL-C relationship was inverted U-shaped in males and approximately linear in females.

Introduction

Higher body mass index (BMI), as an indicator of overweight and obesity, troubled more and more people worldwide and caused serious public health concern. It has been shown that, by 2030, the prevalence of overweight and obese will be increase to 23% and 32% respectively [1]. Overweight and obesity has affected all ages especially for the elderly adults, and closely associated with the occurrence of metabolic disorders and cardiovascular disease (CVD) [2, 3]. One study found that for every 5 kg/m² increased in BMI, the average of all-cause mortality and vascular mortality would increase by 30% and 40% separately [4].

Metabolic syndrome (MS) as one of the causes of CVD that associated with higher BMI and dyslipidemia which contributed by elevated triglycerides and reduced low-density lipoprotein cholesterol (HDL-C), but without a clear alter of low-density lipoprotein cholesterol (LDL-C) [5]. However, a large body of epidemiology and Mendelian randomization studies have suggested that LDL-C is a well-established risk factor for CVD [6]. Moreover, compared with HDL-C and triglyceride, the concentration of LDL-C and its therapeutic modification are greater associated with CVD [7–9].

Previous studies are mainly explored the linear relationship between LDL-C and BMI in the small or selected samples, remaining limited data on potential sex differences. For example, a study performed in the US population suggested that LDL-C was linearly related to BMI [10]. Another study conducted with US children group also indicated that BMI was strong determinants of lipid and lipoprotein levels [11]. While one study showed that LDL-C only increased with greater BMI among younger subjects, but not among men over 50 years [12]. Most notably, a recent study investigated both US and Spain large population found that there is not always a linear relationship between LDL-C and BMI, i.e., age and metabolic status play essential roles and effects on relationship. However, although visceral fat area was found positively correlated with serum LDL-C levels in a nondiabetic Chinese population [13], the association between BMI and LDL-C are yet to be clearly defined, and further research about the sex difference in above association is still needed since the distribution of fat differed between sex.

This study is aimed to explore the sex differences in the nonlinear relationship between BMI and LDL-C in the Chinese adult population and stratified by age groups and MS status. The findings could help to provide a detailed dose-response relationship between LDL-C and BMI, shedding lights on the prevention and treatment of CVD.

Methods

Study Population

We analyzed two cross-sectional nationally representative datasets in China from the China Health and Nutrition Survey (CHNS) and the China Health and Retirement Longitudinal Study (CHARLS). Detailed descriptions of these two studies have been published [14, 15]. Briefly, the CHNS is an ongoing open cohort designed to monitor and understand the association between socio-economic factors and health change in China [14]. The CHNS was initially conducted in 1989, while the biomarker data was first collected in 2009. The CHARLS is a nationally representative longitudinal study conducted in 2011-12 from 150 counties of 28 provinces in China, with information on demographic characteristics, medical history, lifestyles, and laboratory testing on a set of individuals [15]. Written informed consents were obtained from all participants from CHNS and CHARLS.

In the current study, we identified all adults aged 45 to 75 years with the availability data of blood biomarkers and anthropometric measures in both these two datasets. Furthermore, participants with missing baseline covariates or having cardiovascular disease or cancer were excluded. Finally, a total of 12273 participants ($n = 4788$ for CHNS; $n = 7485$ for CHARLS) were included in the final analysis (Fig. 1).

Measures

Information on age, sex, residence (urban or rural), education level ($<$ high school or $\geq$ high school), marital status (married or others), current smoking and drinking status (yes or no), and medical history and drugs use were obtained from the standard questionnaires and harmonized for both two datasets. Blood samples were obtained and measured for serum lipids (total cholesterol, triglycerides, LDL-C, HDL-C) and blood glucose. Data on anthropometry (BMI and waist circumference [WC]) and blood pressure were measured with standard methods. The cardiometabolic health was defined as the number of MS criteria (excluding the WC criterion) enlisted in the harmonized joint MS definition [16].

Statistical analysis

Participant characteristics by sex were described in the pooled database and separately in CHARLS and CHNS. Differences between sexes in continuous variables were assessed using the Student's t-test or Mann-Whitney U test and in categorical variables using Pearson's χ^2 test.

To explore the nonlinear relationship between BMI and LDL-C in women and men, generalized additive models (GAMs) with a factor-smooth interaction between sex (factor) and BMI (smooth function) were fitted. Models were adjusted for age, residence, education levels, marital status, drinking, smoking status, and cohort sources. Thus, model can be expressed as follows:

$$Y_i = \beta_0 + \left[f_{BMI}, \text{SEX} \left(BMI_i \right) \times I \left(x_{\text{sex}} = 1 \right) \right] + \left[f_{BMI}, \bar{\text{sex}} \left(BMI_i \right) \times I \left(x_{\text{sex}} = 0 \right) \right] + \beta_{\text{sex}} x_{\text{sex}} + \beta \text{Cov}_i^T + \epsilon_i$$

where Y_i is the response of LDL-C for individual i , f_{BMI} is the nonparametric smooth function of BMI, $\beta_{\text{sex}} x_{\text{sex}}$ is the main effect of the predictor variable sex, βCov_i^T is the linear predictor of covariables, and ϵ_i is the error terms, which are assumed to be normally distributed. Then we performed the multivariable adjusted generalized linear model using linear

splines, with the break points identified from GAMs smooth plot. In addition, to describe how the relationship between BMI and LDL-C varied according to age and cardiometabolic health, we also performed GAMs stratified by the age-groups (45–54, 55–64, 65–75 years) and the number of MS criteria (excluding the WC criterion).

All analyses were performed using Stata 16.0 (Stata Corp LLC, College Station, Texas, US) and the gam function of “mgcv” package in the R statistical software (version 4.0.2). Two-tailed *P* values < 0.05 were considered statistically significant.

Results

Baseline characteristics

A total of 12273 adults (6493 females and 5780 males) aged 45–75 years were included in this analysis. Table 1 shows the characteristics of study population by sexes. There were significant differences in female and male in age, education level, marital status, smoking, drinking, diastolic blood pressure, BMI, WC, glucose, triglycerides, HDL-C, and count of MS criteria ($P < 0.005$). Baseline characteristics stratified by CHARLS and CHNS are showed in the **Supplementary File Table S1**.

Relationship of BMI and LDL-C

Table 2 shows the estimated regression coefficients from the GAMs with the factor-smooth interaction terms for sex*BMI. The interaction sex*BMI, older age, residence, and education were statistically significantly associated with LDL-C. The estimated smooth functions in Fig. 2 shows the nonlinear relationship between BMI and LDL-C in female and male ($P < 0.001$ for smooth terms). Table 3 shows the results from generalized linear models using linear splines. In female, BMI was linearly associated with LDL-C below a BMI of 22.5 kg/m² (slope: 2.14, 95% CI: 1.42 to 2.86); and followed a plateau at BMI values of 22.5–27.5 kg/m² (slope: 0.38, 95% CI: -0.22 to 0.98); then gradually increased after BMI of 27.5 kg/m² (slope: 0.68, 95% CI: -0.31 to 1.67). In male, the association between BMI and LDL-C is inverse U-shaped, with the break point at BMI of 27.5 kg/m² (slope: 1.77, 95% CI: 1.43 to 2.11 for BMI < 27.5 kg/m²; slope: -1.84, 95% CI: -3.01 to -0.66 for BMI ≥ 27.5 kg/m²).

Subgroup Analysis

The nonlinear relationship between BMI and LDL-C in female and male were obvious in all age-groups and only with 1 of MS criteria (**Figure S1 and Figure S2 in the Supplementary File**).

Discussion

In this study, we measured the dose-response relationship of BMI and LDL-C in Asian population, and further explored the association between BMI and LDL-C in sex subgroup and different MS status. It has been found that, in the population with normal or light weight ($\text{BMI} < 22.5 \text{ kg/m}^2$), the association between BMI and LDL-C was linearly and positively correlated, in the overweight population, with the increase of BMI, the level of LDL-C gradually tended to be flat or even decreased. The trend of the above association was also different between genders, and the inverted-U shape was showed in male.

The association between BMI and lipid metabolites was assessed chiefly in HDL-C or triglyceride levels with the result of linear association, but the dose-response relationship of BMI and LDL-C has occasionally been carried out and the result remains inconsistent. Several studies have indicated a positive association between BMI and LDL-C [17–20], whereas

representative data from the U.S. and Spain found an inverted U-shaped association between BMI or WC and LDL-C [6], which is consistent with a similar study with the nondiabetic American Indians [22]. In addition, some studies suggested that association between BMI and LDL-C differ between sex and age subgroup [20, 23]. Although the above studies have initially pointed out the association between BMI and LDL-C, it is limited to the European and American population, and most of the studies only explored the single sex. This study based on the Chinese population, estimating the ascending and descending slopes, as well as inflection points, comprehensively discussing the association between BMI and LDL-C in sex, age, and MS status subgroups.

The results of the present study suggested that, based on the Chinese population, the association between BMI and LDL-C showed as an inverted U-shape, which is consistent with previous two studies conducted with the U.S. and Spain populations [6, 22]. While WC and LDL-C showed as an inclined S-shape. The above epidemiological findings have also been supported by the studies of biological mechanisms. In particular, in non-obese people ($\text{BMI} < 25 \text{ kg/m}^2$), triglycerides are converted into cholesterol rich intermediate density lipoprotein (IDL) and LDL for adipogenesis, leading a positive correlation between BMI and LDL in the lean individuals [6]. However, triglycerides may be stored in very low density lipoprotein (VLDL) when lipid deposition in adipose tissue reaches the maximum limit or other exists lipid metabolism disorders, resulting in a decrease in the formation of LDL [24]. Another possible explanation is that adipose tissue store large amounts of cholesterol, thus buffering the cholesterol load of the liver [25]. A study has pointed out that the secretion of bile cholesterol in obese people increases gradually with the accumulation of adipose cell [26]. Therefore, in obese people, normal LDL-C levels may suggest that increased adipocytes are maintaining cholesterol homeostasis. In addition, our study first found that the association between WC and LDL-C showed as an inclined S-shape, which is inconsistent with the association between BMI and LDL-C and the results of previous study. It is well known that the obesity types and fat distribution of Asians and Westerners are different. In addition, with the increase of weight, adipose cell is more likely to accumulate in the abdomen for men, while it is more likely to accumulate in the lower body for woman [27]. Therefore, the gender ratio of the included population will lead to differences in results. Taken together, both ethnic differences and the sex ratio of the recruited subjects may cause the inconsistency, however, more direct evidence of the underlying mechanism regarding the association will be needed.

The performance of the association between BMI and LDL-C in sex subgroup has also been investigated. The inverted U-shape is obviously showed in the male group while it disappeared in the female group. The majority of studies on the above-mentioned associations are carried out in a single sex, especially in men. Moreover, previous study suggested that, after avoiding the confounding factor of body fat percentage, the association of physical fitness level and that plasma lipid profiles between male and female is different [28]. In addition, subjects included in our study are over 45 years old, and a study indicated that the level of LDL-C has been affected by menopausal status, i.e., post-menopause female have higher concentrations of LDL-C [29–31]. Thus, we assume that differences in hormonal status between male and female may lead to different associations between BMI and LDL-C. Some studies have shown that BMI and LDL-C have a positive linear relationship in female. Quantitative studies have also shown that LDL-C of female with BMI between 27.1 kg/m^2 and 30.0 kg/m^2 increased by 17 mg/dl compared with subjects whose BMI between 21.1 kg/m^2 and 23.0 kg/m^2 [23]. This study also found that LDL-C increased with BMI, moreover, it is first time showed that there were two turning points in the association between BMI and LDL-C, that is, the slope began to flatten near the edge of obesity, and gradually increased again when BMI reached 27.0 kg/m^2 . Although we speculate that hormonal status may be responsible for above association, the specific mechanism remains to be further investigated.

Our results supported that the MS status played a role in the association between BMI and LDL-C, i.e., with aggravation of metabolic impairment (number of MS criteria), the turning point of the association curve between BMI and LDL-C gradually appeared earlier. In the extreme group that the subjects had three or four MS criteria, the association trend in male was weakened, while it was more unstable in female. Similar results have been reported in the US population

Loading [MathJax]/jax/output/CommonHTML/fonts/TeX/fontdata.js subgroups separately and provided a thorough and detailed

dose-response relationship between BMI and LDL-C. It is well known that MS is related to the increase of BMI. A study even pointed out that MS is caused by the abnormal function of adipose tissue, that is, adipose tissue reached the limit of functional capacity. Another reason may be that, in the regulation of homeostasis mechanism, lipid transport cholesterol may reduce the risk of diabetes and produce high levels of LDL-C. However, after the homeostasis mechanism broken, abnormal cholesterol synthesis and transport will also break the linear relationship between BMI and LDL-C.

Two limitations of this study are addressed. First, this study is a cross-sectional study, which is not able to explain the causal relationship between BMI and LDL-C. Second, in this study, the number of MS criteria was used to represent the severity of MS, where need more accurate quantitative indicators to explore the association between BMI and LDL-C.

Conclusions

Our study suggested LDL-C increased with BMI in both female and male lean individuals. Trends of the dose-response curve of BMI and LDL-C changed slightly in the different sexes, ages, and MS status. Overall, reducing BMI may lower the level of LDL-C to some extent, which is beneficial to the prevention of CVD.

Declarations

Conflicts of Interest: None.

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Tables

Table 1
Baseline Characteristics by Sex in CHARLS and CHNS

	Female (n = 6493)	Male (n = 5780)	P value
Age, years, mean (SD)	57.16 (8.06)	57.91 (8.07)	< 0.001
45–54	2642 (40.69)	2148 (37.16)	
55–64	2536 (39.06)	2331 (40.33)	
65–75	1315 (20.25)	1301 (22.51)	
Rural residence, n (%)	4302 (66.26)	3896 (67.40)	0.18
High school or above, n (%)	694 (10.69)	1054 (18.24)	< 0.001
Married, n (%)	5411 (83.34)	5218 (90.28)	< 0.001
Drinking, n (%)	741 (11.41)	3461 (59.88)	< 0.001
Smoking, n (%)	340 (5.24)	3449 (59.67)	< 0.001
Body mass index, kg/m ² , mean (SD)	23.89 (3.53)	23.13 (3.31)	< 0.001
Waist circumference, cm, mean (SD)	83.88 (11.47)	84.30 (11.15)	0.040
Systolic BP, mmHg, mean (SD)	129.02 (20.97)	129.42 (19.22)	0.26
Diastolic BP, mmHg, mean (SD)	77.73 (12.02)	79.09 (12.49)	< 0.001
Glucose (mg/dl), mean (SD)	121.82 (34.99)	113.65 (34.19)	< 0.001
LDL cholesterol (mg/dl), mean (SD)	105.25 (33.34)	106.43 (34.17)	0.052
Triglycerides (mg/dl), median (IQR)	114.17 (80.54, 165.49)	103.54 (72.57, 160.18)	< 0.001
HDL cholesterol (mg/dl), mean (SD)	53.97 (16.49)	52.62 (18.73)	< 0.001
Count of MS criteria, n (%)			< 0.001
0	965 (14.86)	961 (16.63)	
1	1936 (29.82)	1951 (33.75)	
2	1777 (27.37)	1685 (29.15)	
3 or 4	1815 (27.95)	1183 (20.47)	
Cohort			0.32
CHARLS	3933 (60.57)	3552 (61.45)	
CHNS	2560 (39.43)	2228 (38.55)	
BP = blood pressure, CHARLS = China Health and Retirement Longitudinal Study, CHNS = China Health and Nutrition Survey, MS = metabolic syndrome, LDL = low density lipoprotein, HDL = high density lipoprotein, SD = standard deviation, IQR = interquartile range.			

Table 2

Estimated regression coefficients (β) from the generalized additive model with a factor-smooth interaction

		CHARLS data		CHNS data		Pooled data	
		β (SE)	P value	β (SE)	P value	β (SE)	P value
Intercept		100.71 (3.27)	< 2e-16	107.32 (4.53)	< 2e-16	105.12 (2.7)	< 2e-16
Age	Per 1 year	0.34 (0.05)	1.04e-11	0.35 (0.07)	1.03e-07	0.36 (0.04)	< 2e-16
Sex	Female	Reference		Reference		Reference	
	Male	-6.13 (1.05)	5.74e-09	-7.47 (1.39)	7.53e-08	-6.67 (0.84)	1.79e-15
Sex*BMI (smooth)	Female	See Fig. 2 (A)	3.88e-08	See Fig. 2 (B)	2.76e-07	See Fig. 2 (C)	2.22e-14
	Male	See Fig. 2 (A)	3.97e-14	See Fig. 2 (B)	1.57e-13	See Fig. 2 (C)	< 2e-16
Residence	Urban	Reference		Reference		Reference	
	Rural	$\bar{x}$ -0.27 (0.83)	0.750	$\bar{x}$ -4.76 (1.18)	5.30e-05	$\bar{x}$ -1.88 (0.68)	0.006
Education	Below high school	Reference		Reference		Reference	
	High school or above	0.33 (1.32)	0.805	1.27 (1.39)	0.358	1.26 (0.94)	0.180
Marital status	Others	Reference		Reference		Reference	
	Married	$\bar{x}$ -0.56 (1.32)	0.617	0.22 (1.65)	0.892	$\bar{x}$ -0.36 (0.93)	0.702
Smoking	No	Reference		Reference		Reference	
	Yes	$\bar{x}$ -1.11 (1.06)	0.294	$\bar{x}$ -0.48 (1.42)	0.734	$\bar{x}$ -0.8 (0.85)	0.343
Drinking	No	Reference		Reference		Reference	
	Yes	$\bar{x}$ -1.22 (1.32)	0.188	$\bar{x}$ -0.78 (1.34)	0.562	$\bar{x}$ - 1.08 (0.77)	0.158
Cohort	CHNS					Reference	
	CHARLS					3.90 (0.64)	1.41e-09
		R-sq.(adj) = 0.0299		R-sq.(adj) = 0.0419		R-sq.(adj) = 0.0381	

Table 3

Slopes (95% CIs) of the association of BMI with LDL cholesterol among individuals below or above the inflection point

BMI (kg/m ²)			LDL cholesterol slope (mg/dL per kg/m ²) ¶ *		
	Inflection point 1	Inflection point 2	Lower range (95% CI) (below inflection point 1)	Middle range (95% CI) (Between inflection point 1 and 2)	Upper range (95% CI) (above inflection point 2)
Female	22.5	27.5	2.14 (1.42 to 2.86)	0.38 (-0.22 to 0.98)	0.68 (-0.31 to 1.67)
Male	27.5	NA	1.77 (1.43 to 2.11)	NA	-1.84 (-3.01 to -0.66)

¶ The slopes estimation using the generalized linear models using linear splines.

* Adjusted for age, sex, residence, education levels, marital status, drinking, smoking status, and cohort.

Figures

Figure 1

Figure 2

The nonlinear relationship between BMI and LDL-C in female and male using generalized additive models with the factor-smooth interaction terms for sex*BMI.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementary20210804.docx](#)