

BMJ Open Joint effects of serum ferritin and body mass index on the risk of coronary artery disease: a case-control study

Yunping Zhou,¹ Tongtao Liu,² Chongqi Jia¹

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¹Department of Epidemiology and Health Statistics, Shandong University, Jinan, Shandong, People's Republic of China

²Department of Cardiology, Qilu Hospital, Shandong University, Jinan, Shandong, People's Republic of China

Correspondence to

Chongqi Jia;
jiachongqi@sdu.edu.cn

ABSTRACT

Objectives: Serum ferritin and body mass index (BMI) have been reportedly associated with coronary artery disease (CAD) risk. The aim of the present study was to explore the interaction between serum ferritin and BMI on CAD risk.

Design: Hospital-based case-control study.

Setting: Patients with CAD and the controls were recruited from Qilu Hospital, Shandong University.

Participants: 258 CAD cases and 282 healthy controls.

Methods: Multiplicative interaction was assessed through a cross-product interaction term in a multivariate logistic regression model. The effect of serum ferritin and BMI were evaluated per 50 µg/L and per 2 kg/m², respectively. The presence of additive interaction between serum ferritin and BMI was evaluated by calculation of the relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP) and synergy index (S).

Results: The ORs and 95% CI of the serum ferritin-BMI product term on a multiplicative scale in the univariate and multivariate models were 0.943 (0.904 to 0.984) and 1.004 (0.951 to 1.059), respectively. There was also evidence for interaction on an additive scale; the RERI (95% CI), AP (95% CI) and S (95% CI) in the univariate model were 0.314 (0.026 to 1.506), 0.107 (0.017 to 0.241) and 1.194 (1.053 to 1.406), respectively. After adjusting for the potential confounders, the estimates and 95% CIs for the aforementioned three measures were 0.004 (−0.016 to 0.311), 0.004 (−0.016 to 0.191) and 1.039 (0.774 to 1.285), respectively.

Conclusions: Serum ferritin and BMI had an additive interaction on the risk of CAD in Chinese population. Further investigations with big sample size are necessary for confirming this additive interaction.

INTRODUCTION

Coronary artery disease (CAD) is the main cause of death worldwide,¹ and the burden of cardiovascular diseases in many countries continues to rise.² Identifying and characterising the modifiable risk factors for CAD remains important for public health and clinical

Strengths and limitations of this study

- To our knowledge, this is the first study to explore the interaction between elevated serum ferritin and increased body mass index (BMI) for the risk of coronary artery disease.
- Since this was only a hospital-based case-control study, selection bias might exist and could distort the association.
- The evidence for interaction should be interpreted cautiously because our hypothesis of serum ferritin-BMI interaction was tested retrospectively. Unknown confounders may lead to overestimation or underestimation of the interaction.

medicine. CAD is a chronic disease of multifactorial origin that develops from the interplay of lifestyle (smoking, physical activity, diet, etc), physiological (age, gender, menopausal status, etc), genetic and other factors.^{3 4}

In 1981, Sullivan⁵ proposed the 'iron hypothesis', indicating that body iron overload was positively associated with CAD risk. The mechanism underlying this hypothesis was that elevated iron levels were related with increased free radical production and elevated oxidative stress.⁶ Serum ferritin, a major iron storage protein and the best biochemical measure of body iron stores,⁷ is essential to iron homeostasis, and it is involved in a wide range of physiological and pathological processes.⁸

Obesity, measured by body mass index (BMI) is considered as the largest public health problem worldwide, especially in industrialised countries.^{9 10} Obesity increases the mortality and the prevalence of cardiovascular diseases, diabetes and other health problems.^{11 12} Accumulating evidence indicates that obesity plays a key role in atherosclerosis mainly through oxidative stress,¹³ including generation of reactive oxygen species, deficiency of antioxidant defence mechanisms¹⁴ and endothelial dysfunction, which is known as a prognostic for cardiovascular risk.¹⁵

Since serum ferritin and BMI have been shown to be independently associated with CAD risk, the hypothesis is that there should be an interaction between serum ferritin and BMI on CAD risk. However, to our knowledge, little information is now available for this interaction. Thus, in the present study, we explore the biological interaction between serum ferritin and BMI on CAD risk.

METHODS

Study design

The present hospital-based case–control study included 258 newly diagnosed patients with CAD and 282 healthy controls. All the patients with CAD were recruited from the Department of Cardiology, Qilu Hospital, Shandong University. The diagnosis of CAD is defined according to the WHO criteria¹⁶ and described briefly below: more than 50% of stenosis in at least one major coronary artery determined by percutaneous coronary angiography; symptoms, ECG changes and elevation of cardiac enzymes for myocardial infarction; symptoms and ECG changes for arrhythmias and angina pectoris. The 282 controls were recruited from the healthy persons examined in the Physical Examination Center at Qilu Hospital. All participants were asked to fill out a questionnaire regarding their lifestyle. BMI was calculated as weight (kg) divided by squared height (m²). The blood samples were obtained from the remnants of the venous blood for the participant's laboratory tests. All participants provided informed consent.

Laboratory analysis methods

Serum ferritin and 8-iso-prostaglandin F_{2α} (8-iso-PGF_{2α}) concentrations were measured by the ELISA method, using a commercial kit (Blue Gene, Shanghai, China). Serum triglyceride (TG) and total cholesterol (TC) were measured by enzymatic colorimetric method on a Hitachi 717S automatic biochemical analyser.

Statistical analysis

One-way analysis of variance was used to test the differences of means for continuous variables, and Pearson's χ^2 test was performed to compare the categorical variables between cases and controls. Multiplicative interaction was assessed through serum ferritin–BMI interaction term in the univariate and multivariate logistic regression models. The effect of serum ferritin and BMI was evaluated per 50 $\mu\text{g/L}$ and per 2 kg/m^2 , respectively. The variables of smoking, alcohol intake and hypertension were defined as dichotomous variables. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg or a history of hypertension. The variables of age, serum TG, TC and 8-iso-PGF_{2α} were treated as continuous variables, and were in the multivariate logistic regression model plus sex, smoking, alcohol intake and hypertension as the potential confounders.

Interaction as departure from additivity was assessed by three measures: relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP)

and synergy index (S), which were presented by Rothman and described previously.¹⁷ The bootstrap percentile method¹⁸ taking 10 000 bootstrap samples (with replacement) from the original dataset and each of which being the same size as the original sample was used to calculate the CIs for the three aforementioned measures. The RERI, AP and S were then estimated in each of these new samples and the 95% CI for the three measures were estimated as the 2.5th and 97.5th centiles of the resulting bootstrap sampling distribution. All statistical analyses were performed with STATA V.12 (Stata Corporation, College Station, Texas, USA). All reported probabilities (p values) were two sided, with $p < 0.05$ considered as statistically significant.

RESULT

Study characteristics

The demographic characteristics of the case–control study are summarised in table 1. The traditional CAD risk factors such as age and hypertension in the CAD group were significantly higher than those in the controls. Serum 8-iso-PGF_{2α} levels (an indicator for oxidative stress¹⁹) in the CAD group are significantly higher than that in the control group. The mean BMI was 26.05 kg/m^2 in the cases, and 25.11 kg/m^2 in the controls ($p = 0.002$). Mean and range of serum ferritin concentrations were 170.21 $\mu\text{g/L}$ (2.52–860.55 $\mu\text{g/L}$) in the cases and 149.42 $\mu\text{g/L}$ (7.19–529.49 $\mu\text{g/L}$) in the controls ($p = 0.064$).

Effect of interaction between serum ferritin and BMI on CAD

Table 2 shows that per 50 $\mu\text{g/L}$ increase of ferritin and per 2 kg/m^2 increase of BMI, the risk of having CAD

Table 1 Baseline characteristics of CAD cases and controls

Variables	Case participants (n=258)	Control participants (n=282)	p Value
Age (years)	59.59±9.59	47.64±10.23	0.000
Sex (male, %)	69.38	52.84	0.000
Hypertension (%)	62.79	33.33	0.000
Smoke (%)	47.47	31.58	0.000
Alcohol (%)	28.79	47.37	0.000
8-iso-PGF _{2α} (ng/mL)	1.35±1.88	0.82±0.80	0.000
Diabetes (%)	22.09	0.36	0.000
TC (mmol/L)	4.72±1.09	5.03±0.94	0.000
TG (mmol/L)	1.66±0.75	1.50±1.12	0.053
BMI (kg/m^2)	26.05±3.29	25.11±3.66	0.002
Ferritin level ($\mu\text{g/L}$)	170.21±147.20	149.42±112.32	0.064

All values are expressed as mean±SD or percentage.

p Values between CAD and control groups.

8-iso-PGF_{2α}, 8-iso-prostaglandin F_{2α}; BMI, body mass index; CAD, coronary artery disease; TC, total cholesterol; TG, triglycerides.

Table 2 Output of logistic regression model with SF (per 50 µg/L) as cont determinant, BMI (per 2 kg/m²) as cont determinant and product of age and BMI entered into the model

Parameter	Male		Female		Total	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Model 1*						
SF (per 50 µg/L) cont	1.137 (0.548 to 2.361)	0.730	3.396 (1.076 to 10.722)	0.037	2.217 (1.276 to 1.177)	0.005
BMI (per 2 kg/m ²) cont	1.082 (0.831 to 1.411)	0.558	1.558 (1.189 to 2.043)	0.001	1.403 (1.177 to 1.672)	0.000
SF cont×BMI cont	0.988 (0.935 to 1.045)	0.673	0.916 (0.837 to 1.004)	0.060	0.943 (0.904 to 0.984)	0.007
Model 2†						
SF (per 50 µg/L) cont	0.921 (0.404 to 2.099)	0.845	2.188 (0.588 to 8.142)	0.243	1.241 (0.658 to 2.340)	0.504
BMI (per 2 kg/m ²) cont	1.054 (0.776 to 1.430)	0.738	1.300 (0.949 to 1.782)	0.102	1.175 (0.960 to 1.439)	0.118
SF cont×BMI cont	1.010 (0.948 to 1.075)	0.765	0.931 (0.841 to 1.032)	0.174	0.989 (0.942 to 1.038)	0.661
Model 3‡						
SF (per 50 µg/L) cont	0.987 (0.380 to 2.560)	0.978	2.069 (0.502 to 8.539)	0.314	0.999 (0.493 to 2.025)	0.997
BMI (per 2 kg/m ²) cont	1.233 (0.861 to 1.765)	0.253	1.122 (0.780 to 1.614)	0.534	1.101 (0.869 to 1.395)	0.424
SF cont×BMI cont	1.008 (0.939 to 1.083)	0.818	0.929 (0.832 to 1.037)	0.192	1.004 (0.951 to 1.059)	0.894

Outcome is coronary artery disease.

*Not adjusted for other covariates.

†Adjusted for age.

‡Adjusted for age, smoking, alcohol intake, hypertension, total cholesterol; triglycerides and 8-iso-PGF2 α . 8-iso-PGF2 α , 8-iso-prostaglandin F2 α ; Cont, continuous; BMI, body mass index; SF, serum ferritin.

increased with a factor of 2.217 and 1.403, respectively. The ORs (95% CI) of the product term for interaction on a multiplicative scale were female: 0.916 (0.837 to 1.004); male: 0.988 (0.935 to 1.045); and total population: 0.943 (0.904 to 0.984). After adjusting for potential covariates, the ORs (95% CI) of the product term for multiplicative interaction were female: 0.929 (0.832 to 1.037); male: 1.008 (0.939 to 1.083); and total population: 1.004 (0.951 to 1.059).

Results of additive interaction are shown in table 3. An additive interaction was found in the univariate model (female: RERI=0.895, 95% CI 0.006 to 13.531; AP=0.184, 95% CI 0.005 to 0.415; S=1.303, 95% CI 1.042 to 1.769; male: RERI=-0.003, 95% CI -0.022 to 0.491; AP=

-0.003, 95% CI -0.017 to 0.219; S=0.985, 95% CI 0.804 to 1.294; total population: RERI=0.314, 95% CI 0.026 to 1.506; AP=0.107, 95% CI 0.017 to 0.241; S=1.194, 95% CI 1.053 to 1.406). The RERI of 0.314 in total population means that with every 50 µg/L increase in ferritin and 2 kg/m² increase in BMI, the relative risk of having CAD is 0.314 more than if there were no interaction. After adjusting for potential confounders, a positive interaction was found between serum ferritin and BMI on an additive scale (female: RERI=-0.033, 95% CI -0.412 to 12.725; AP=0.009, 95% CI -0.014 to 0.174; S=0.972, 95% CI 0.535 to 1.531; male: RERI=0.007, 95% CI -0.061 to 1.215; AP=0.006, 95% CI -0.075 to 0.396; S=1.032, 95% CI 0.596 to 1.647; total population:

Table 3 Additive interactions between SF (per 50 µg/L) and BMI (per 2 kg/m²)

Parameters	Male	Female	Total estimates (95% CI)
Interaction model 1*			
RERI	-0.003 (-0.022 to 0.491)	0.895 (0.006 to 13.531)	0.314 (0.026 to 1.506)
AP	-0.003 (-0.017 to 0.219)	0.184 (0.005 to 0.415)	0.107 (0.017 to 0.241)
S	0.985 (0.804 to 1.294)	1.303 (1.042 to 1.769)	1.194 (1.053 to 1.406)
Interaction model 2†			
RERI	0.005 (-0.017 to 0.507)	0.162 (-0.084 to 8.477)	0.026 (-0.008 to 0.408)
AP	0.005 (-0.017 to 0.531)	0.061 (-0.067 to 0.342)	0.018 (-0.008 to 0.134)
S	0.801 (0.766 to 1.344)	1.109 (0.759 to 1.606)	1.064 (0.803 to 1.275)
Interaction model 3‡			
RERI	0.007 (-0.061 to 1.215)	-0.033 (-0.412 to 12.725)	0.004 (-0.016 to 0.311)
AP	0.006 (-0.075 to 0.396)	0.009 (-0.014 to 0.174)	0.004 (-0.016 to 0.191)
S	1.032 (0.596 to 1.647)	0.972 (0.535 to 1.531)	1.039 (0.774 to 1.285)

Data are estimates (95% CI).

*Not adjusted for other covariates.

†Adjusted for age.

‡Adjusted for age, smoking, alcohol intake, hypertension, total cholesterol; triglycerides and 8-iso-PGF2 α .

8-iso-PGF2 α , 8-iso-prostaglandin F2 α ; AP, attributable proportion due to interaction; BMI, body mass index; RERI, relative excess risk due to interaction; S, synergy index; SF, serum ferritin.

RERI=0.004, 95% CI -0.016 to 0.311; AP=0.004, 95% CI -0.016 to 0.191; S=1.039, 95% CI 0.774 to 1.285).

Robustness of RERI and CI

To assess the robustness of RERI and 95% CI in the univariate model, we calculated the RERI (95% CI) using different units of increase in serum ferritin (20, 50 and 100 µg/L) and different units of increase in BMI (2, 3, 4 and 5 kg/m²). The results are presented in table 4. With the increasing units in serum ferritin and BMI increased, the additive interaction also increased. For example, the RERI with serum ferritin per 20 µg/L increase and BMI per 2 kg/m² increase was 0.106, while the RERI with serum ferritin per 100 µg/L increase and BMI per 5 kg/m² increase was 4.559 (table 4).

DISCUSSION

CAD is a multifactorial chronic disease that develops from the interplay of genetic, lifestyle, physiological and other factors; a well understanding of the interaction between these risk factors is important to identify the target groups for CAD. In our previous study,²⁰ serum ferritin was found to be an independent risk factor of CAD, and several studies²¹ have reported that obesity could elevate serum ferritin levels. However, whether there is an interaction of BMI with serum ferritin levels and CAD risk, and the extent to which the interaction influences the CAD risk are still unknown, and no study has reported the biological interaction of serum ferritin and BMI with CAD risk so far. Thus, in the present study, we explored the possible biological interaction of serum ferritin levels and BMI with CAD risk, and found evidence of additive interaction. This finding provided further evidence that iron overload to the risk of CAD appeared to be most significant among persons with higher BMI.

Previous studies have demonstrated the independent pathogenic role of BMI²²⁻²⁴ in the development of CAD. Regarding serum ferritin, a study conducted in a large Korean population²⁵ sample also indicated that ferritin

was independently associated with the presence of coronary artery calcium. Since both factors have been shown to be independently associated with CAD risk, there should be an interaction between elevated serum ferritin levels and increased BMI on CAD risk. RERI, one measure of additive interaction, refers to the excess risk due to interaction relative to the risk without exposure. RERI>0 indicated a positive interaction or more than additivity. In this study, the RERI of 0.314 in total population means that with the increase of serum ferritin and BMI, the relative risk of having CAD is 0.314 more than if there were no interaction. Therefore, the risk conferred by one of the factors is increased by the presence of the other one. This is clinically important because previous observational studies and clinical trials have suggested an increased risk of CAD with elevated serum ferritin. And the additive interaction between serum ferritin and BMI indicated that the CAD risk in obesity patients with elevated serum ferritin would be higher than that in patients with lower BMI. Besides, weight control by physical activity may also decrease the CAD risk in patients with higher serum ferritin.

Concepts of interaction play an important role in epidemiological data analysis and interpretation. From public health and clinical perspectives, a well understanding of the interaction between serum ferritin and BMI is important to implement primary prevention strategies for CAD. A cross-sectional study²⁶ has shown that the association between cardiovascular arteriosclerotic disease and serum ferritin was partially caused by BMI and other confounders. Besides, Crist *et al*²⁷ suggested that elevated ferritin concentration is associated with an increased risk of CAD, possibly due to the interaction of adiposity, which accelerates atherogenesis by stimulating oxidative stress. Therefore, it could be reasonable that there was biological interaction between serum ferritin and BMI. Our results supported this speculation, and revealed an additive interaction between serum ferritin and BMI on CAD risk. From the viewpoint of prevention and clinical practice, additive interaction is more important than multiplicative interaction, as it could better reflect biological interaction.²⁸

In the explanation of our results, the limitations in our study should be taken into consideration. First, since this was only a hospital-based case-control study, selection bias might exist and could distort the association. Generally, the sample size for interaction analysis for case-control study should be much more than that for the traditional case-control study. Therefore, the second limitation was the relative small sample size; this was why the CIs of RERI were much broader. Third, ORs, instead of risk ratios, were used to assess the additive interaction of the three measures (RERI, AP and S). Kalilani and Atashili²⁹ suggested that this substitution may be erroneous under some conditions. However, this effect is likely to be little in our study, since the baseline incidence of CAD in general population is relatively low. Fourth, the evidence for interaction should be interpreted

Table 4 RERI and 95% CI for different units increase in serum ferritin (20, 50 and 100 µg/L) and BMI (2, 3, 4 and 5 kg/m²)

RERI (95% CI)	SF (µg/L)		
	20	50	100
BMI (kg/m ²)			
2	0.106 0.011 to 0.417	0.314 0.026 to 1.506	1.186 0.090 to 8.285
3	0.118 0.006 to 0.544	0.596 0.057 to 2.933	2.126 0.156 to 15.683
4	0.209 0.018 to 0.982	0.930 0.097 to 5.025	3.240 0.260 to 27.606
5	0.462 0.052 to 2.034	1.559 0.147 to 8.530	4.559 0.309 to 38.090

BMI, body mass index; RERI, relative excess risk due to interaction; SF, serum ferritin.

cautiously because our hypothesis of serum ferritin–BMI interaction was tested retrospectively. Unknown confounders may lead to overestimation or underestimation of the interaction.

Despite these limitations, an additive interaction between serum ferritin and BMI was detected in our study. Further investigations with big sample size are necessary for confirming this additive interaction and elucidating the exactly underlying mechanism that will shed light on the prevention of CAD.

Contributors YZ and TL did the data analyses and drafted the manuscript. CJ contributed to the design of the research, interpretation of results and the revision of the manuscript. The manuscript was reviewed and approved by all the authors prior to submission.

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Competing interests None.

Patient consent Obtained.

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