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Obesity and hypertension are independent risk factors for the development of interatrial block

Running Title: Obesity, hypertension and interatrial block

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Abstract

Objectives: This study was to characterize the independent influences of obesity and hypertension on interatrial block (IAB) after adjusting for cardiovascular risk factors and echocardiographic left atrial diameter (LAD) in a large general Chinese population.

Design: A cross-sectional study.

Setting and participants: A total of 11,956 permanent residents of Liaoning Province in China ≥ 35 years of age was conducted. All participants completed the questionnaire, physical exams, laboratory analyses, echocardiography and electrocardiography. Logistic regression analyses were performed to estimate the crude and independent associations between risk factors and the prevalence of IAB.

Outcome measures: IAB was defined as a prolongation of the P-wave duration ≥120 milliseconds on the 12-lead ECG. Hypertension was defined as a systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg and/or the use of antihypertensive medications according to the JNC-7 Guidelines. As recommended by the Working Group on Obesity in China, overweight and obesity was defined as a BMI of 24.0–27.9, ≥28.0 kg/m^2, respectively.

Results: The prevalence of IAB in hypertensive subjects was higher than normotensive in both men (9.5 *vs*. 5.9%; $P < 0.001$) and women (6.6 *vs*. 3.6%; $P < 0.001$). In addition, IAB prevalence rose steeply with advancing body mass index (BMI) in both men (from 4.9 to 13.0%) and women (from 3.5 to 6.9%) (*P*s for trend < 0.001). After adjusting for multiple relevant clinical covariates and echocardiographic LAD, the stepwise logistic regression analysis shown that hypertension was independently associated with IAB prevalence (OR = 1.35; 95%CI: 1.13–1.62), and the prevalence of IAB was significantly higher in both

overweight (OR = 1.49; 95%CI: 1.23–1.81) and obese subjects (OR = 1.82; 95%CI: 1.44–2.28), compared with BMI < 24.0 kg/m^2.

Conclusions: Obesity/overweight and hypertension were independent and significant risk factors for IAB in the general Chinese population.

Key words: Interatrial block; Obesity/overweight; Hypertension

Strengths and limitations of this study:

- This study assessed the independent influences of obesity and hypertension on IAB in a large general Chinese population.
- Besides multiple clinical covariates, echocardiographic LAD was also adjusted in the logistic regression analysis.
- This study was a single-center design and only permanent residents ≥ 35 years of age were enrolled.
- This was a cross-sectional study and further prospective ones should be conducted.

Introduction

Interatrial block (IAB) is characterized by the presence of a prolonged P-wave that exceeds 120 ms on a 12-lead electrocardiogram (ECG) [1], which is widely used in periodic health examination and almost all clinical departments. However, reports about the prevalence of IAB described this condition as being an under-appreciated clinical pandemic, particularly in the males and aging population [2-4]. IAB has been proved to be associated with a multitude of medical conditions including atrial arrhythmias [5-7], abnormality in left atrial function [8], and thromboembolic ischemic stroke [9-12]. According to a further follow-up study, advancing P-wave duration was significantly associated with increasing cardiovascular and all-cause mortality [13]. Therefore, as an important predictor for long-term outcome, great efforts should be made to demonstrate the prevalence of IAB and associated risk factors.

As we known, obesity and hypertension have a high prevalence and often coexist, leading to left atrial enlargement. Previous studies have shown that they appear to be risk factors for IAB, but these studies were conducted in general hospital patients admitted for nonacute reasons with a small sample size [14 15]. According to the ARIC study (Atherosclerosis Risk in Communities Study), obesity and metabolic syndrome (particularly with hypertension) were significantly positively associated with IAB independent of age and cardiovascular risk factors [16]. However, they did not take left atrial diameter (LAD) into account. Therefore, whether their associations with IAB were dependent on the changes of echocardiographic LAD has never been analyzed. Further, there have no large sample size study focused on the risk factors for IAB in Chinese population. Thus, the purpose of this study was to assess the independent influences of obesity and hypertension on IAB after

adjusting for cardiovascular risk factors and echocardiographic LAD in a large general Chinese population.

Materials and methods

Study population

From January 2013 to August 2013, a representative sample of men and women in Liaoning Province was evaluated for the presence of cardiovascular risk factors (mainly hypertension) using a multi-stage, randomly stratified, cluster-sampling scheme, which is called Northeast China Rural Cardiovascular Health Study (NCRCHS). For the purpose of hypertension and related cardiovascular study, a representative sample aged ≥ 35 years was selected. And our current study about IAB was part of the NCRCHS. Three counties (Dawa, Zhangwu, and Liaoyang) were selected from the eastern, southern, and northern regions of Liaoning Province, where most of residents are agricultural laborers. One township near a city in each county was randomly selected for a total of three townships, and six to eight villages from each township were randomly selected for a total of 26 rural villages. Those who were pregnant, had cancer or mental disorders were excluded from the study.

All the eligible permanent residents ≥35 years of age from each village (n = 14,016) were invited to participate, of which 11,956 (85.3%) completed the study. Subjects with incomplete data, poor ECG quality, atrial fibrillation/flutter on the ECG, or atrial paced rhythm were excluded from the study, leaving a total of 11,271 participants for the final analyses. The study was approved by the Ethics Committee of China Medical University in Shenyang, China, and all procedures were performed in accordance with its ethical standards.

Written consent was obtained from all participants after they had been informed of the study's objectives, benefits, medical procedures and confidentiality safeguards for personal information. If the participants were illiterate, we obtained written informed consent from their proxies.

Data collection and measurements

Data were collected during a single clinic visit by cardiologists and trained nurses using a standard questionnaire in a face-to-face interview. All potential investigators had received training on the objectives of the study, how to administer the questionnaire, the standard methods of measurement, the importance of standardization, and study procedures. Only those who earned a perfect score on a post-training test were allowed to participate as study investigators. During data collection, the inspectors received further instructions and support. Data on demographic characteristics, medical history, and lifestyle risk factors were obtained, as described above, by interview with the standardized questionnaire. There was a central steering committee with a subcommittee for quality control that made sure all data were collected according to well-known standards.

According to the American Heart Association, blood pressure (BP) was measured three times at two-minute intervals after at least five minutes of rest using a standardized automatic electronic sphygmomanometer (HEM-907; Omron, Kyoto, Japan). Two doctors checked the calibration of the Omron device every month using a standard mercury sphygmomanometer according to the British Hypertension Society protocol [17]. The participants were advised to avoid caffeinated beverages and to exercise for ≥ 30 min before the measurement. During the measurement, the participants were seated with their arms supported at the level of their

hearts. The mean of three BP measurements was calculated and used in all analyses. Hypertension was defined as a systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg and/or the use of antihypertensive medications according to the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) Guidelines [18]. Weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, with the participants in lightweight clothing without shoes. The body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). As recommended by the Working Group on Obesity in China, overweight was defined as a BMI of 24.0–27.9 kg/m^2, and obesity as a BMI of 28.0 kg/m^2 or higher [19].

Fasting blood samples were collected in the morning after ≥ 8 h of fasting for all participants. Blood samples were obtained from an antecubital vein using BD Vacutainer tubes containing EDTA (Becton, Dickinson and Co., Franklin Lakes, NJ, USA). Serum was subsequently isolated from whole blood, and all serum samples were frozen at -20°C for testing at a central, certified laboratory. Fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), high density lipid cholesterol (HDL-C), low density lipid cholesterol (LDL-C), serum uric acid (SUA), and other routine blood biochemical indices were analyzed enzymatically on an auto-analyzer (Olympus AU640 Auto-Analyzer; Olympus Corp., Kobe, Japan). According to the World Health Organization criteria, diabetes mellitus was defined as a FBG ≥ 7.0 mmol/L, and/or being on treatment for diabetes [20].

Twelve-lead resting, ten-second ECGs were performed on all participants by well-trained cardiologists using an electrocardiography machine (MAC 5500; GE Healthcare, Little Chalfont, Buckinghamshire, UK). The results were analyzed automatically by the

MUSE Cardiology Information System (version 7.0.0; GE Healthcare). The P-wave onset was defined as the point of initial upward or downward deflection from the isoelectric line and the offset was defined as the return of the waveform to the initial baseline. According to the most recent consensus guidelines [1], IAB was defined as a prolongation of the P-wave duration ≥120 milliseconds on the 12-lead ECG in our current study.

Echocardiograms were obtained using a commercially available Doppler echocardiograph (Vivid; GE Healthcare) with a 3.0-MHz transducer. Echocardiogram analyses and readings were performed by three doctors specialized in echocardiography, and two other specialists were called in if questions or uncertainty arose. LAD in the current study was the left atrial anteroposterior measurement in the parasternal long-axis view according to the recommendations of the American Society of Echocardiography [21].

Statistical analysis

All statistical analyses were conducted with SPSS 17.0 statistical software (SPSS, Inc., Chicago, IL, USA). Differences between groups were compared using a two-tailed Student's t-test for continuous variables and a χ^2 test for categorical variables. IAB prevalence by BMI category and hypertension were calculated and presented. Univariate, multivariate and stepwise logistic regression analyses were performed to evaluate the associations between selected risk factors and the presence of IAB. Interaction regression models were used to test the effects of hypertension or overweight/obesity on the other's association with IAB prevalence. Data are presented as odds ratio (OR) and 95% confidence interval (CI), mean ± standard deviation, or frequency and percentages; a $P < 0.05$ was considered as statistically significant.

Results

Characteristics of the study population

The 11,271 participants for final analyses were comprised of 5,127 men and 6,144 women with a mean age of 53.8 years. The subjects with IAB (n = 712) were significantly older and had higher BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), FBG, TC, TG, LDL-C, SUA and LAD than those with normal P wave duration (all Ps < 0.05) (Table 1). In addition, the participants with IAB had significantly higher percentage of men and current drinker, and higher prevalence of obesity, hypertension and diabetes mellitus (all Ps < 0.05). Whereas, the level of HDL-C was lower in subjects with IAB than those without IAB (P = 0.002). However, there was no significant difference in smoking status between the two groups (P = 0.736).

IAB prevalence by hypertension and BMI category

Gender-specific prevalences of IAB by hypertension and BMI category were listed in Figure 1. The prevalence of IAB in hypertensive subjects was higher than normotensive in both men (9.5 *vs*. 5.9%; P < 0.001) and women (6.6 *vs*. 3.6%; P < 0.001). In addition, the prevalence of IAB rose steeply with advancing BMI in both men (4.9, 9.0, 13.0% in those with BMI < 24.0, 24.0–27.9, ≥ 28.0 kg/m^2, respectively; P for trend < 0.001) and women (3.5, 5.9, 6.9% in those with BMI < 24.0, 24.0–27.9, ≥ 28.0 kg/m^2, respectively; P for trend < 0.001). Prevalence of IAB for BMI category by hypertension was also calculated and presented in Figure 2. As a result, the prevalence of IAB rose significantly with advancing BMI in both normotensive and hypertensive subjects (Ps for trend < 0.001). Further, it was

higher in the hypertensive subgroup at each BMI category (all *P*s < 0.05).

Factors associated with IAB

Several clinical characteristics were significant predictors of IAB in age- and gender-adjusted regression models (Table 2). The ORs and 95%CI were 1.17 (1.09–1.25) by decade increasing of age and 1.58 (1.35–1.84) for male than female participants. Compared with BMI < 24.0 kg/m^2, the prevalence of IAB was significantly higher in subjects with BMI 24.0–27.9 kg/m^2 (OR = 1.86; 95%CI: 1.55–2.23) and BMI > 30.0 kg/m^2 (OR = 2.56; 95%CI: 2.09–3.15). It was also found that IAB prevalence was significantly higher in hypertensive than normotensive subjects (OR = 1.67; 95%CI: 1.41–1.97). In addition, TC, TG, LDL-C, SUA and LAD were all significantly associated with higher prevalence of IAB (all *P*s < 0.05), whereas HDL-C and current smoking were correlated with lower IAB prevalence (*P*s < 0.05). However, diabetes and drinking status had no significant influence on IAB.

A stepwise logistic regression analysis revealed that advancing age, male sex, overweight/obesity, hypertension, and increasing LAD were significant independent risk factors for IAB (all *P*s < 0.05) (Table 3). Variables excluded in the stepwise logistic regression analysis were diabetes, TC, TG, LDL-C, HDL-C, SUA, and current smoking and drinking status. Interaction logistic regression analyses showed that the influence of BMI and hypertension on each other's association with IAB was not being statistically significant (*P* = 0.414).

Discussion

To our knowledge, this is the largest (*n* = 11,271) assessment of the risk factors for IAB

in the general Chinese population. Obesity and hypertension are pandemic and often coexisting, and we found a higher prevalence of IAB in subjects with hypertension and advancing BMI. Hypertension additionally increased the prevalence of IAB among individuals with overweight and obesity. Further, it was shown that both obesity and hypertension significantly and independently aggravated the risk of IAB even after adjusting for multiple clinical covariates and echocardiographic LAD.

Our findings on the risk factors for IAB are consistent with those findings reported in the ARIC[16] and Multiethnic Study of Atherosclerosis (MESA) studies [22]. ARIC study reported that IAB is significantly associated with obesity and hypertension independent of age and cardiovascular risk factors in a cross-sectional population-based analysis [16], supporting our findings. The subgroup analysis of the Multiethnic Study of Atherosclerosis (MESA) also confirmed our results, showing that increased BMI was associated with IAB after adjusting for age, sex, ethnicity and pericardial fat [22]. However, both of the two studies' examination of BMI, hypertension and IAB did not adjust for echocardiographic LAD. In contrast, our study was strengthened by comprehensive adjustment for cardiovascular risk factors and echocardiographic LAD in our multivariable analyses.

According to our study, the influence of obesity and hypertension on IAB was independent of echocardiographic LAD. This meant that the prolongation of P wave duration may be earlier than left atrial enlargement or at least not consistent. Our finding is supported by Antoni Bayés de Luna who proposes the concept of "Bayes' syndrome". He stated that the potential pathophysiology of IAB is directly related to a block in the area of Bachmann's bundle. Although atrial enlargement and IAB share a similar electrocardiographic pattern,

they are two separate entities [1] [23] [24]. The mechanism of hypertension and obesity's associations with IAB is likely multifactorial [25]. Obesity and hypertension increase cardiac loading, resulting in compensatory remodeling [26], and obesity induces paracrine hormone expression with endovascular effects that may also alter atrial pressures and loading conditions [27] [28]. These reveal the role of LAD in the impacts of obesity and hypertension on IAB. On the other hand, insulin resistance, as the basis of metabolic syndrome, has cellular and electrophysiologic effects by affecting metabolic function, including impairment of mitochondrial function and oxidative stress [29]. Obesity could directly drive electrophysiologic remodeling by altering the myocardial matrix secondary to adipose-derived hormones [30] [31]. Therefore, the influence of obesity and hypertension on IAB is not totally depending on LAD. These explained our finding that obesity and hypertension had independent impacts on IAB.

This study has several limitations. First, the cross-sectional design does not examine the longitudinal associations between obesity/hypertension and IAB. Similarly, the cross-sectional design of the study is unable to distinguish causality between obesity, hypertension and IAB. Second, the prevalence of IAB in each stages of hypertension in our study was too small so that we had no subgroup analysis for the trends of BP levels. Finally, it was a single-center design only including subjects ≥ 35 years of age and all the enrolled participants were from the same one province in China. Therefore, the representativeness of the sample is relatively limited.

Conclusion

In this study, there was a higher prevalence of IAB in subjects with hypertension and

advancing BMI. Hypertension additionally increased the prevalence of IAB among individuals with each BMI category. Further, both obesity/overweight and hypertension significantly and independently increased the prevalence of IAB even after adjusting for multiple relevant covariates and echocardiographic LAD.

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Conflicts of interest

None.

Authors' contributions

GZS collected the data, analyzed and prepared the first draft of the manuscript. YZ supervised the data collection and reviewed the manuscript. NY coordinated the data collection. SJW did the data analyses. YXS conceived the study design, reviewed the final manuscript and serves as guarantor for the contents of this paper. All authors approved the final version.

Data sharing statement

The data is available from the corresponding author on reasonable request.

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Table 1. Characteristics of the study population

Variable	IAB - (*n* = 10,559)	IAB + (*n* = 712)	*P* value
Age, years	53.6 ± 10.6	55.5 ± 10.2	< 0.001
Male	4,725 (44.7)	402 (56.5)	< 0.001
Height, cm	160.3 ± 8.2	163.1 ± 8.0	< 0.001
Weight, kg	63.7 ± 11.3	69.2 ± 11.6	< 0.001
BMI, kg/m^2	24.7 ± 3.7	25.9 ± 3.6	< 0.001
BMI category, kg/m^2			< 0.001
< 24	4,757 (45.1)	207 (29.1)	
24–28	3,990 (37.8)	315 (44.2)	
≥ 28	1,812 (17.2)	190 (26.7)	
SBP, mmHg	141.3 ± 23.3	149.3 ± 24.9	< 0.001
DBP, mmHg	81.7 ± 11.6	85.7 ± 12.8	< 0.001
Hypertension	5,290 (50,1)	459 (64.5)	< 0.001
FBG, mmol/L	5.88 ± 1.61	6.08 ± 1.75	0.003
Diabetes	1,068 (10.1)	89 (12.5)	0.042
TC, mmol/L	5.22 ± 1.07	5.37 ± 1.31	0.003
TG, mmol/L	1.62 ± 1.49	1.86 ± 1.65	< 0.001
LDL-C, mmol/L	2.92 ± 0.81	3.03 ± 0.93	0.001
HDL-C, mmol/L	1.41 ± 0.38	1.37 ± 0.38	0.002
SUA, mg/dL	4.87 ± 1.42	5.22 ± 1.45	< 0.001

Variable	IAB - (*n* = 10,559)	IAB + (*n* = 712)	*P* value
Current smoker	3,714 (35.2)	466 (34.6)	0.736
Current drinker	2,313 (21.9)	196 (27.5)	< 0.001
LAD, mm	33.6 ± 3.9	35.4 ± 4.5	< 0.001

Abbreviations: BMI = body mass index; DBP = diastolic blood pressure; FBG = fasting blood glucose; HDL-C = high density lipid cholesterol; IAB = interatrial block; LAD = left atrial diameter; LDL-C = low density lipid cholesterol; SBP = systolic blood pressure; SUA = serum uric acid; TC = total cholesterol; TG = triglycerides.

Note: data are expressed as mean ± standard deviation or *n* (%).

Table 2. Associations between various clinical parameters and IAB.

Variable	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)*	P value
Age, per 10 years	1.18 (1.10–1.27)	< 0.001	1.17 (1.09–1.25)	< 0.001
Male vs. Female	1.60 (1.37–1.87)	< 0.001	1.58 (1.35–1.84)	< 0.001
BMI category, kg/m^2				
< 24	1		1	
24–28	1.81 (1.52–2.17)	< 0.001	1.86 (1.55–2.23)	< 0.001
≥ 28	2.41 (1.97–2.96)	< 0.001	2.56 (2.09–3.15)	< 0.001
Hypertension (yes/no)	1.81 (1.54–2.12)	< 0.001	1.67 (1.41–1.97)	< 0.001
Diabetes (yes/no)	1.27 (1.01–1.60)	0.043	1.22 (0.96–1.54)	0.098
TC, per mmol/L	1.13 (1.06–1.21)	< 0.001	1.12 (1.05–1.20)	0.001
TG, per mmol/L	1.08 (1.04–1.12)	< 0.001	1.07 (1.04–1.11)	< 0.001
LDL-C, per mmol/L	1.18 (1.08–1.29)	< 0.001	1.17 (1.07–1.28)	< 0.001
HDL-C, per mmol/L	0.72 (0.58–0.89)	0.002	0.71 (0.58–0.88)	0.002
SUA, per mg/dL	1.17 (1.12–1.23)	< 0.001	1.12 (1.06–1.18)	< 0.001
Current smoker (yes/no)	0.97 (0.83–1.14)	0.736	0.77 (0.64–0.91)	0.003
Current drinker (yes/no)	1.35 (1.14–1.61)	0.001	1.08 (0.89–1.32)	0.423
LAD, per cm	3.03 (2.51–3.64)	< 0.001	2.73 (2.26–3.30)	< 0.001

Abbreviations: CI = confidence interval; OR = odds ratio; others as in Table 1.

Note: * adjusted for age and gender.

Table 3. Stepwise logistic regression analysis of risk factors for IAB (Forward)

Variable	OR (95% CI)	*P* value
Age, per 10 years	1.11 (1.02–1.20)	0.011
Male vs. Female	1.41 (1.20–1.65)	< 0.001
BMI category, kg/m^2		*
< 24	1	
24–28	1.49 (1.23–1.81)	< 0.001
≥ 28	1.82 (1.44–2.28)	< 0.001
Hypertension (yes/no)	1.35 (1.13–1.62)	0.001
LAD, per cm	2.08 (1.69–2.56)	< 0.001

Abbreviations as in Table 1 and 2.

Note: *P = 0.414 for the interaction of BMI category and hypertension.

Figure legends

Figure 1. Gender-specific prevalence of interatrial block (IAB) by hypertension and body mass index (BMI) category.

Figure 2. Prevalence of interatrial block (IAB) for body mass index (BMI) category by hypertension.

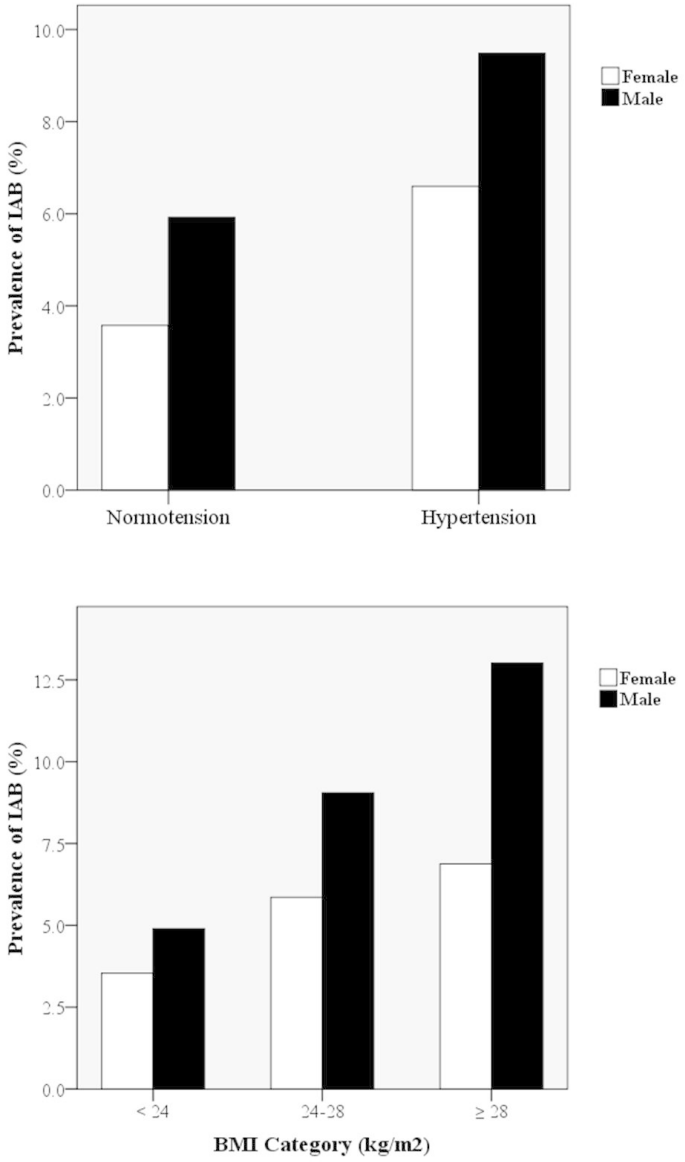

Figure 1. Gender-specific prevalence of interatrial block (IAB) by hypertension and body mass index (BMI) category.

170x273mm (150 x 150 DPI)

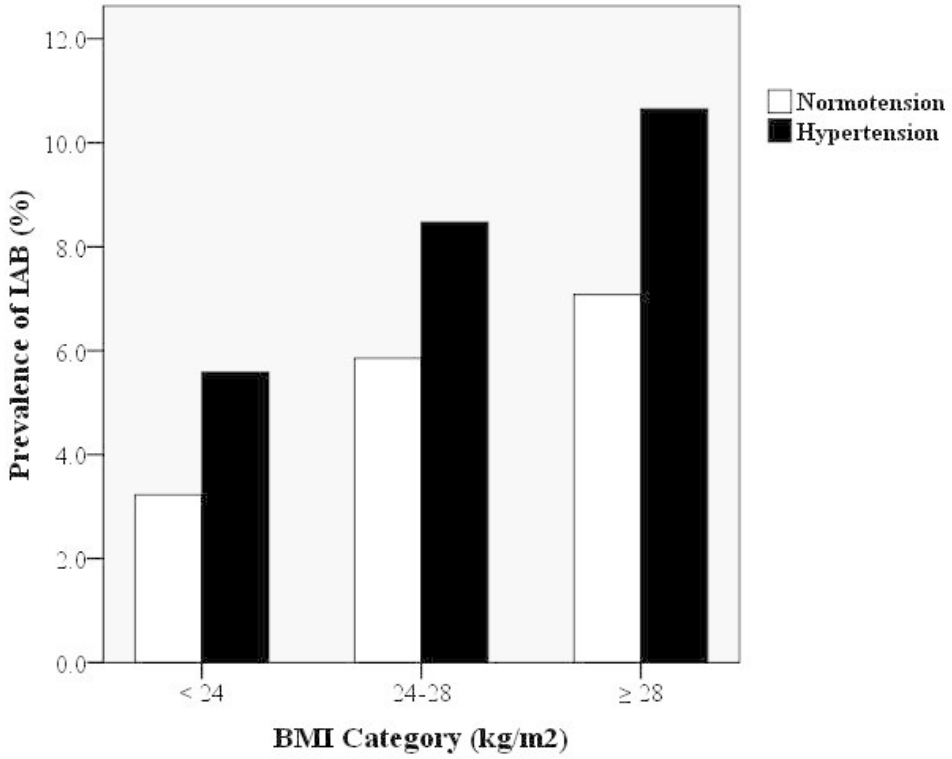

Figure 2. Prevalence of interatrial block (IAB) for body mass index (BMI) category by hypertension.

167x134mm (96 x 96 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, 10
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
Outcome data	15*	Report numbers of outcome events or summary measures	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	10-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Hypertension and obesity are independently related to interatrial block: A cross-sectional study in a general Chinese population

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Hypertension and obesity are independently related to interatrial block: A cross-sectional study in a general Chinese population

Running Title: Hypertension, obesity and interatrial block

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Abstract

Objectives: This current study was performed to characterize the independent associations of obesity and hypertension with interatrial block (IAB) after adjusting for cardiovascular risk factors, echocardiographic left atrial diameter (LAD) and left ventricular mass index (LVMI) in a large general Chinese population.

Design: A cross-sectional study.

Setting and participants: A total of 11,956 permanent residents (≥ 35 years of age) from Liaoning Province in China were recruited for this study. Following the completion of a questionnaire, the enrolled participants were subjected to physical examinations, laboratory analyses, electrocardiogram (ECG) as well as echocardiogram. Linear and logistic regression analyses were performed to evaluate the independent associations of hypertension and obesity with IAB.

Outcome measures: IAB was defined as a prolongation of the P-wave duration ≥120 milliseconds on the digital 12-lead ECG.

Results: The prevalence of IAB in hypertensive individuals was higher than the normotensive in both men (9.5 *vs*. 5.9%; $P < 0.001$) and women (6.6 *vs*. 3.6%; $P < 0.001$). In addition, the prevalence of IAB displayed a sharp increase with advancing BMI in both men (from 4.9 to 13.0%) and women (from 3.5 to 6.9%) (*P*s for trend < 0.001). Multiple relevant clinical covariates, LAD and LVMI were adjusted in the multivariate linear and logistic regression

analyses. As a result, SBP, DBP and BMI were all independently associated with P wave duration (β = 0.02, 0.09 and 0.25, respectively; all *P*s < 0.005). Furthermore, hypertension was independently associated with IAB (OR = 1.27; *P* = 0.018), while both overweight and obesity had higher odds of IAB (OR = 1.42 and 1.67, respectively; *P*s < 0.005), compared with BMI < 24.0 kg/m^2.

Conclusions: The key findings of the current study highlighted that hypertension and overweight/obesity were independently and significantly associated with IAB in a general Chinese population.

Key words: Interatrial block; Hypertension; Overweight/obesity.

Strengths and limitations of this study:

- The current study evaluated the independent associations of hypertension and overweight/obesity with IAB.
- This was a large population-based study, providing adequate data and sample size to delineate the study objective.
- Digital ECG was an important strength since automatic measures had superior validity and reliability compared to manual readings.
- Besides multiple clinical covariates, echocardiographic LAD and LVMI were also adjusted in multivariate logistic regression analyses.
- This was a cross-sectional study and further prospective ones should be conducted.

Introduction

Interatrial block (IAB) is characterized by the presence of a prolonged P-wave exceeding 120 ms on a 12-lead electrocardiogram (ECG) [1]. Accumulating reports have highlighted the prevalence of IAB as an under-appreciated clinical issue, particularly in the male and aging populations [2-4]. Existing literature has provided evidence linking IAB with a multitude of medical conditions including atrial arrhythmias [5-7], abnormal left atrial function [8], and thromboembolic ischemic stroke [9-12]. A follow-up study suggested that an advancing P-wave duration was significantly associated with an increasing risk of cardiovascular and all-cause mortality [13]. Therefore, as a potentially crucial predictor of long-term patient outcome, additional efforts are required in order to further elucidate the prevalence of IAB and its associated risk factors.

Obesity and hypertension with high prevalence continue to strain clinical resources, both of which may lead to left atrial enlargement. Previous studies have implicated both obesity and hypertension as risk factors for IAB, but many of these studies were conducted in general hospitals with patients admitted for non-acute issues with small sample sizes [14 15]. The Atherosclerosis Risk in Communities (ARIC) study demonstrated that both obesity and metabolic syndrome (particularly with hypertension) correlated with IAB, independent of age and other cardiovascular risk factors [16]. However, these studies have failed to take the left atrial diameter (LAD) into account. Hence, the current study set out to examine whether these associations with IAB were dependent on echocardiographic LAD changes, an investigation of

which is yet to be conducted. In addition, there have been no large sample size studies emphasizing the risk factors contributing to IAB in Chinese population. Thus, the central objective of this study was to assess the independent associations of obesity and hypertension with IAB after adjusting for cardiovascular risk factors and echocardiographic changes in a large general Chinese population.

Materials and methods

Study population

Between January 2013 and August 2013, a representative sample of men and women from Liaoning Province were evaluated for cardiovascular risk factors (mainly hypertension) using a multi-stage, random, stratified, cluster-sampling scheme, referred to as the Northeast China Rural Cardiovascular Health Study (NCRCHS). This study intentionally enrolled a representative sample aged ≥ 35 years, due to its purpose of evaluating hypertension and related cardiovascular risk factors. Three counties (Dawa, Zhangwu, and Liaoyang) were selected from the eastern, southern, and northern regions of Liaoning Province, where the greater majority of residents are agricultural laborers. One township near a city in each county was randomly selected, totaling three townships, and five to eight villages from each township were randomly selected, with 18 rural villages finally selected. Those who were pregnant, suffering from cancers or mental disorders were excluded from this study.

All eligible permanent residents ≥35 years of age from each village (n = 14,016) were recruited for this study, with 11,956 (85.3%) participants having completed the study. Subjects with incomplete data, poor ECG quality, atrial fibrillation/flutter, paced rhythm, WPW syndrome, or congenital heart disease were excluded from the study, leaving a total of 11,264 participants for the final analyses. The study was performed under the approval of the Ethics Committee of China Medical University in Shenyang, China. All the procedures were conducted in strict accordance with its ethical standards. All participants signed written consent after they had been informed of the study's objectives, benefits, medical procedures and confidentiality safeguards for personal information. Also, informed consent was obtained from the proxies of participants who were illiterate.

Data collection and measurements

Data were collected during a single clinic visit by cardiologists and trained nurses by means of a standard questionnaire in a face-to-face interview. All the potential investigators had received training in relation to the objectives of the study, how to perform the questionnaire, the standard methods of measurement, the importance of standardization, as well as the finer details of the study procedures. Only those who earned a perfect score on a post-training test were permitted to participate as study investigators. During the process of data collection, the investigators were provided with additional instructions and support. Data on demographic characteristics, medical history, and lifestyle risk factors were obtained, as described above, by means of an interview with a standardized questionnaire. A central steering committee with a

subcommittee for quality control ensured that all data were collected in accordance with the aforementioned standards.

According to the guidelines of the American Heart Association, blood pressure (BP) was measured three times at two-minute intervals, with a resting period of at least five minutes using a standardized automatic electronic sphygmomanometer (HEM-907; Omron, Kyoto, Japan). Two doctors checked the calibration of the Omron device every month using a standard mercury sphygmomanometer in accordance with the British Hypertension Society protocol [17]. All participants were advised to avoid caffeinated beverages and exercise at least 30 min prior to evaluation. During the measurement, the participants were seated with their arms supported at the level of their hearts. The mean value of three BP measurements were calculated and used in all the subsequent analyses. Hypertension was defined by the criteria widely employed and considered to be the worldwide standard in epidemiological research studies: a systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg and/or the use of antihypertensive medications. All participants were classified into the following groups based on mean SBP/DBP and the most recent 2017 ACC/AHA guidelines [18]: (a) normal: SBP < 120 mmHg and DBP < 80 mmHg, (b) Elevated BP: SBP 120–129 mmHg and DBP < 80 mmHg, (c) Stage 1 hypertension: SBP 130–139 mmHg or DBP 80–89 mmHg, and (d) Stage 2 hypertension: SBP ≥ 140 mmHg or DBP ≥ 90 mmHg. During the course of the study, subjects who were taking anti-hypertensive medication and had a history of hypertension were considered to be at stage 2 hypertension as their BP levels would have exceeded 140/90 mmHg

during their initial hypertension diagnosis in accordance with the previous criteria. Weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, with all participants given lightweight clothing and evaluated barefoot. The body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). As recommended by the Working Group on Obesity in China, overweight was defined as a BMI of 24.0–27.9 kg/m^2, and obesity as a BMI of 28.0 kg/m^2 or higher [19].

Fasting blood samples were collected in the morning after ≥ 8 h of fasting. Blood samples were collected from the antecubital vein using BD Vacutainer tubes containing EDTA (Becton, Dickinson and Co., Franklin Lakes, NJ, USA). Serum was subsequently isolated from whole blood, with all serum samples subsequently frozen at -20°C for testing at a central, certified laboratory. Fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), high density lipid cholesterol (HDL-C), low density lipid cholesterol (LDL-C), serum uric acid (SUA), and other routine blood biochemical indices were analyzed enzymatically on an auto-analyzer (Olympus AU640 Auto-Analyzer; Olympus Corp., Kobe, Japan). According to the criteria issued by World Health Organization, diabetes mellitus was defined as a FBG ≥ 7.0 mmol/L, and/or patients currently being treated for diabetes [20].

Twelve-lead resting, ten-second ECGs were performed on all participants by well-trained cardiologists using an electrocardiography machine (MAC 5500; GE Healthcare, Little Chalfont, Buckinghamshire, UK). The results were automatically analyzed by the MUSE Cardiology Information System (version 7.0.0; GE Healthcare). The P wave in each lead was

defined as the initial upward point or downward deflection from the isoelectric line to the point of the initial baseline. For the calculation of the P wave duration, onsets were defined as the earliest deflection in any lead, and offsets were defined as the latest deflection in any lead. Based on the most recent consensus guidelines [1], IAB was defined as a prolonged P-wave duration ≥120 milliseconds on a 12-lead ECG in our current study.

Echocardiograms were obtained using a commercially available Doppler echocardiograph (Vivid; GE Healthcare) with a 3.0-MHz transducer. Echocardiogram analyses and readings were performed by three separate doctors, all of whom were specialized in echocardiography, with two other specialists called in case of any questions or uncertainties. LAD in the current study was the left atrial anteroposterior measurement in the parasternal long-axis view according to the recommendations of the American Society of Echocardiography [21]. The reported LAD values in our study were not indexed by body surface area. Left ventricular mass index (LVMI) was calculated based on body surface area, while left ventricular hypertrophy (LVH) was defined as a LVMI > 115 g/m^2 in males and > 95 g/m^2 in females.

Statistical analysis

All statistical analyses were performed using SPSS 17.0 statistical software (SPSS, Inc., Chicago, IL, USA). Differences between groups were compared using a two-tailed Student's *t*-test for continuous variables and a χ^2 test for categorical variables. IAB prevalence by BMI category and hypertension were calculated and presented accordingly. Multivariate linear regression analyses were performed to identify the linear correlation between BP, BMI and P

wave duration. Multivariate logistic regression analyses were conducted to evaluate the link between hypertension and obesity with IAB. Data were expressed as odds ratio (OR) and 95% confidence interval (CI), β, mean ± standard deviation, or frequency and percentages; A *P* value < 0.05 was considered to be statistically significant.

Patient and public involvement

No patients were involved in setting the research questions or the outcome measures, nor were they involved in the design or performance of the study. No participants or patients were asked to advise on the interpretation or writing up of results. No plans were set in place to disseminate the results of the research to study participants.

Results

Characteristics of the study population

The 11,264 participants for final analyses consisted of 5,126 men and 6,138 women with a mean age of 53.8 years. The general prevalence of IAB was 6.3% (711/11,264) within the total population, which was significantly higher in subjects with left atrial enlargement (LAE) than those without (12.7 *vs*. 5.6%; $P < 0.001$). The subjects with IAB ($n = 711$) were significantly older and had higher BMI, SBP, DBP, FBG, TC, TG, LDL-C, SUA, LAD, LVMI and heart rate than those exhibiting a normal P wave duration (all *P*s < 0.005) (Table 1).

Furthermore, these participants with IAB had significantly higher percentages of men, current drinker, anti-arrhythmic medication and anti-hypertensive medication, and higher prevalences of obesity, hypertension, diabetes mellitus, LAE and LVH (all *P*s < 0.05). Whereas, the level of HDL-C was lower in subjects with IAB than those without IAB (*P* = 0.002). There was no significant difference detected regarding smoking status between the two groups (*P* = 0.699). Furthermore, IAB participants were identified with a relatively higher prevalence of myocardial infarction (MI), heart failure (HF) and mitral stenosis/regurgitation, even though no statistical significance was detected (all *P*s > 0.05).

IAB prevalence by hypertension and BMI category

The gender-specific prevalence of IAB by hypertension and BMI category were shown in Figure 1. The prevalence of IAB in hypertensive subjects was higher than the normotensive in both men (9.5 *vs*. 5.9%; *P* < 0.001) and women (6.6 *vs*. 3.6%; *P* < 0.001). In addition, the prevalence of IAB rose steeply with advancing BMI in both men (4.9, 9.0 and 13.0% in those with BMI < 24.0, 24.0–27.9 and ≥ 28.0 kg/m^2, respectively; *P* for trend < 0.001) and women (3.5, 5.9 and 6.9% in those with BMI < 24.0, 24.0–27.9 and ≥ 28.0 kg/m^2, respectively; *P* for trend < 0.001). The prevalence of IAB for BMI category by hypertension was calculated and presented in Figure 2. Our results demonstrated that the prevalence of IAB rose significantly with advancing BMI in both normotensive and hypertensive subjects (*P*s for trend < 0.001). Furthermore, higher prevalence of IAB was detected in the hypertensive subgroup at each BMI category (all *P*s < 0.05).

Linear relationship of BP, BMI with P wave duration

Multivariate linear regression analyses were performed for the association of BP, BMI and P wave duration, which are presented in Table 2. To better understand the complex effects of the clinical factors associated with the P wave duration, four sets of multivariate models were employed accordingly. In model 1, BP, BMI, age, gender and race were included, with results demonstrating that SBP, DBP and BMI were all independently associated with P wave duration ($\beta = 0.03$, 0.11 and 0.44, respectively; all Ps < 0.001). In model 2, the additional variables FBG, plasma lipids, SUA, smoking, drinking, education, income, anti-arrhythmic medication, anti-hypertensive medication, mitral stenosis/regurgitation and history of MI or HF were also adjusted accordingly, the results of which revealed that the independent associations were presented with a relatively lower β (all Ps < 0.001). In model 3, the linear regression coefficients decreased to 0.02, 0.09 and 0.25 for SBP, DBP and BMI, respectively (all Ps < 0.001) after LAD had been further adjusted. Finally, in model 4, while LVMI was added in the multivariate linear regression, SBP, DBP and BMI were still all found to be independently associated with the P wave duration (all Ps < 0.005).

Associations between hypertension, overweight/obesity and IAB

In an attempt to further evaluate the associations of hypertension and overweight/obesity with IAB, a series of multivariate logistic regression analyses were performed, the results of which are shown in Table 3. In model 1, hypertension, BMI categories, age, gender and race were included, indicating that hypertensive subjects had higher odds of IAB than the

normotensive subjects (OR = 1.42; 95%CI: 1.19−1.68). Compared with individuals with a BMI < 24.0 kg/m^2, higher odds of IAB was found in both overweight (OR = 1.76; 95%CI: 1.46−2.11) and obese individuals (OR = 2.32; 95%CI: 1.88−2.87). In model 2, the additional variables of diabetes, plasma lipids, SUA, smoking, drinking, education, income, anti-arrhythmic medication, anti-hypertensive medication, mitral stenosis/regurgitation, history of MI and history of HF were adjusted accordingly, with the subsequent results obtained indicating that the independent associations preserved with relatively lower ORs (all *P*s < 0.05). In model 3, after LAD had been further adjusted, the ORs decreased to 1.29, 1.40 and 1.64 for hypertension, overweight and obesity, respectively (all *P*s < 0.05). Finally, LVMI was added in model 4, and the ORs became 1.27, 1.42 and 1.67 (all *P*s < 0.05).

Discussion

The current study aimed to conduct the largest evaluation (*n* = 11,264) of the potential factors associated with IAB in a general Chinese population. Our key findings indicated that the prevalence of IAB in China was obviously lower than the American population. Obesity and hypertension are pandemic clinical issues that often coexist. Our results identified a higher prevalence of IAB in subjects with hypertension and advancing BMI. Hypertension additionally increased the prevalence of IAB among individuals with overweight and obesity. Furthermore, observations were made suggesting that both obesity and hypertension were significantly and independently associated with IAB, even after adjusting for multiple clinical covariates,

echocardiographic LAD and LVMI.

An extremely low prevalence of IAB was detected during our study in comparison to previous data[2 4], which may be attributed to the fact that our study population was rural residents with a relatively young mean age. Moreover, it is important to note that the prevalence of atrial fibrillation (AF) in the Asian population is also considerably lower when compared with Western epidemiological and clinical data[22]. Based on the aforementioned analysis, we asserted that IAB might contribute to the relatively low prevalence of AF in China.

Some previous studies have highlighted an association of IAB with obesity[23 24] and hypertension[25-28] . Our findings on the potential risk factors contributing to IAB are consistent with existing literature reported in the ARIC[16] and Multiethnic Study of Atherosclerosis (MESA) studies [29]. ARIC study has reported that IAB is significantly associated with obesity and hypertension, which are independent of age and cardiovascular risk factors in a cross-sectional population-based analysis [16], which was consistent with the findings of this study. The subgroup analysis of the MESA study further confirmed our results, suggesting that increased BMI was associated with IAB after adjusting for age, sex, ethnicity and pericardial fat [29]. However, the examination in both of these two studies on BMI, hypertension and IAB did not adjust for LAD and LVMI. In contrast, a considerable strength of our study was our comprehensive adjustment for echocardiographic LAD and LVMI, in addition to cardiovascular risk factors in the multivariable analyses.

Our key findings revealed that the associations of hypertension and obesity with IAB was

independent of echocardiographic LAD and LVMI, indicating that a prolonged P wave may occur earlier than left atrial enlargement or at least not consistent. The aforementioned finding was supported by the study of Antoni Bayés de Luna who proposed the concept of "Bayes' syndrome". He stated that the potential pathophysiology of IAB was directly related to a block in the area of Bachmann's bundle. Although atrial enlargement and IAB share a similar electrocardiographic pattern, they are two separate entities [1 30 31]. The mechanism underlying the associations of hypertension and obesity with IAB is likely to be multifactorial [32]. Obesity and hypertension increase cardiac preload, resulting in compensatory remodeling [33], with various reports indicating that obesity induces paracrine hormone expression with endovascular effects that may also alter atrial pressures and preload conditions [34 35]. The above finding provides evidence elucidating the role of LAD in relation to the impact of obesity and hypertension on IAB. On the other hand, insulin resistance, as a basic feature of metabolic syndrome, has cellular and electrophysiologic effects by affecting metabolic function, including impairment of mitochondrial function and oxidative stress [36]. Obesity has been reported to directly drive electrophysiologic remodeling by altering the myocardial matrix secondary to adipose-derived hormones [37 38]. Thus, the association of hypertension and obesity with IAB is not totally dependent on LAD and LVMI, providing an explanation for our findings regarding the independent influence of hypertension and obesity on IAB.

This study has several limitations. Firstly, the cross-sectional design does not examine the longitudinal associations of hypertension, obesity with IAB. Besides, the cross-sectional design

of the study is unable to distinguish causality between hypertension, obesity and IAB. Secondly, the detailed information of ECG waveform by automatic measures were unable to be read by the MUSE system, so we did not differentiate between partial and advanced IAB. Thirdly, the sample size in some subgroups by stage of hypertension in our study was relatively small. For example, the number of subjects with elevated stage and IAB was only 54, thus we had no subgroup analysis according to BP stages. Finally, all the enrolled participants were from the same province in China, resulting in a limited representation.

Conclusion

In this study, there was a relatively higher prevalence of IAB in subjects with hypertension and advancing BMI. Hypertension additionally increased the prevalence of IAB among individuals from each BMI category. Furthermore, both hypertension and overweight/obesity significantly and independently increased the prevalence of IAB even after adjusting for multiple relevant covariates, echocardiographic LAD and LVMI.

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Authors' contributions GZS collected the data, analyzed and prepared the first draft of the

manuscript. YZ supervised the data collection and reviewed the manuscript. NY coordinated the data collection. SJW did the data analyses. YXS conceived the study design, reviewed the final manuscript and serves as guarantor for the contents of this paper. All authors approved the final version.

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Conflicts of interest None.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The data is available from the corresponding author upon reasonable request.

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Table 1. Demographic characteristics of the study population

Variable		IAB - (*n* = 10,553)	IAB + (*n* = 711)	*P* value
Age, years		53.6 ± 10.6	55.5 ± 10.2	< 0.001
Male		4,724 (44.8)	402 (56.5)	< 0.001
Race of Han		10,009 (94.8)	668 (94.0)	0.300
Height, cm		160.4 ± 8.2	163.1 ± 8.1	< 0.001
Weight, kg		63.7 ± 11.3	69.2 ± 11.6	< 0.001
BMI, kg/m^2		24.7 ± 3.7	25.9 ± 3.6	< 0.001
BMI category, kg/m^2				< 0.001
	< 24	4,752 (45.0)	206 (29.0)	
	24–28	3,989 (37.8)	315 (44.3)	
	≥ 28	1,812 (17.2)	190 (26.7)	
SBP, mmHg		141.3 ± 23.3	149.4 ± 24.9	< 0.001
DBP, mmHg		81.7 ± 11.6	85.7 ± 12.7	< 0.001
Hypertension		5,288 (50.1)	459 (64.6)	< 0.001
BP category				< 0.001
	Normal	1,657 (15.7)	67 (9.4)	
	Elevated	1,333 (12.6)	54 (7.6)	

Variable	IAB - (*n* = 10,553)	IAB + (*n* = 711)	*P* value
Stage 1 Hypertension	2,275 (21.6)	131 (18.4)	
Stage 2 Hypertension	5,288 (50.1)	459 (64.6)	
FBG, mmol/L	5.88 ± 1.61	6.08 ± 1.75	0.003
Diabetes	1,067 (10.1)	89 (12.5)	0.041
TC, mmol/L	5.22 ± 1.07	5.37 ± 1.31	0.003
TG, mmol/L	1.62 ± 1.49	1.86 ± 1.65	< 0.001
LDL-C, mmol/L	2.92 ± 0.81	3.03 ± 0.93	0.001
HDL-C, mmol/L	1.41 ± 0.38	1.37 ± 0.38	0.002
SUA, mg/dL	4.87 ± 1.42	5.22 ± 1.45	< 0.001
Current smoker	3,712 (35.2)	245 (34.5)	0.699
Current drinker	2,313 (21.9)	196 (27.6)	< 0.001
Education level			0.004
≤ Primary school	5,274 (50.0)	348 (48.9)	
Middle school	4,328 (41.0)	273 (38.4)	
≥ High school	951 (9.0)	90 (12.7)	
Family income, CNY/y			0.281
≤ 5000	1,317 (12.5)	85 (12.0)	

Variable		IAB - (*n* = 10,553)	IAB + (*n* = 711)	*P* value
	5000-20000	5,787 (54.8)	373 (52.5)	
	> 20000	3,449 (32.7)	253 (35.6)	
LAD, mm		33.6 ± 3.9	35.3 ± 4.6	< 0.001
LAE		968 (9.4)	141 (20.4)	< 0.001
LVMI, g/m^2		81.7 ± 19.0	87.7 ± 21.5	< 0.001
LVH		1,047 (10.3)	111 (16.3)	< 0.001
P-wave duration, ms		99.4 ± 12.2	125.6 ± 7.7	< 0.001
Heart rate, bpm		71.5 ± 12.0	73.2 ± 15.5	0.004
Anti-arrhythmic medication		58 (0.5)	9 (1.3)	0.037
Anti-hypertensive medication		1,641 (15.6)	174 (24.5)	< 0.001
History of MI		117 (1.1)	13 (1.8)	0.082
History of HF		84 (0.8)	10 (1.4)	0.083
Mitral stenosis/regurgitation		158 (1.5)	17 (2.4)	0.062

Abbreviations: BMI = body mass index; BP = blood pressure; CNY = China Yuan; DBP = diastolic blood pressure; FBG = fasting blood glucose; HDL-C = high density lipid cholesterol; HF = heart failure; IAB = interatrial block; LAD = left atrial diameter; LAE = left atrial enlargement; LDL-C = low density lipid cholesterol; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; MI = myocardial infarction; SBP = systolic blood pressure; DBP = diastolic blood pressure; SUA = serum uric acid; TC = total cholesterol; TG =

triglycerides.

Note: data are expressed as mean ± standard deviation or *n* (%).

Table 2. Multivariate linear regression analyses for associations between BP, BMI and P-wave duration

	Model 1		Model 2		Model 3		Model 4	
	β	*P* value	β	*P* value	β	*P* value	β	*P* value
SBP, mmHg	0.03	< 0.001	0.03	< 0.001	0.02	< 0.001	0.02	0.002
DBP, mmHg	0.11	< 0.001	0.09	< 0.001	0.09	< 0.001	0.09	< 0.001
BMI, kg/m^2	0.44	< 0.001	0.36	< 0.001	0.25	< 0.001	0.25	< 0.001
Age, year	0.05	0.001	0.05	0.001	0.05	0.001	0.05	0.003
Male (1) *vs*. Female (0)	3.11	< 0.001	2.55	< 0.001	2.02	< 0.001	1.98	< 0.001
FBG, mmol/L	–		0.04	0.614	0.04	0.603	0.04	0.608
TC, mmol/L	–		0.83	0.007	0.73	0.018	0.71	0.023
TG, mmol/L	–		-0.05	0.682	-0.02	0.844	-0.02	0.899
LDL-C, mmol/L	–		-0.36	0.312	-0.21	0.573	-0.17	0.647

HDL-C, mmol/L	–	-1.96	< 0.001	-1.81	< 0.001	-1.81	< 0.001
SUA, mg/dL	–	0.05	0.646	0.01	0.914	0.00	0.994
Current smoker (yes/no)	–	0.02	0.949	0.13	0.663	0.10	0.751
Current drinker (yes/no)	–	1.21	0.001	1.19	0.002	1.18	0.002
LAD, cm	–	–		2.83	< 0.001	2.66	< 0.001
LVMI, g/m^2	–	–		–		0.01	0.208

Abbreviations as in Table 1.

Note: model 1: SBP, DBP, BMI, age, gender and race in the multivariate regression; model 2: additional variables including FBG, plasma lipids, SUA, smoking, drinking, education, income, anti-arrhythmic medication, anti-hypertensive medication, mitral stenosis/regurgitation, and history of MI and HF; model 3: additional variable LAD; model 4: additional variable LVMI.

Table 3. Multivariate logistic regression analyses for associations between hypertension, BMI categories and IAB.

	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Hypertension (Yes/No)	1.42 (1.19–1.68)	< 0.001	1.32 (1.09–1.59)	0.004	1.29 (1.07–1.57)	0.009	1.27 (1.04–1.54)	0.018
BMI < 24 kg/m^2	1		1		1		1	
24–28	1.76 (1.46–2.11)	< 0.001	1.63 (1.35–1.98)	< 0.001	1.40 (1.15–1.72)	< 0.001	1.42 (1.16–1.74)	0.001
≥ 28	2.32 (1.88–2.87)	< 0.001	2.04 (1.62–2.57)	< 0.001	1.64 (1.28–2.10)	< 0.001	1.67 (1.30–2.14)	< 0.001
Age, per 10 years	1.14 (1.06–1.23)	0.001	1.16 (1.07–1.27)	< 0.001	1.14 (1.04–1.24)	0.005	1.12 (1.03–1.23)	0.010
Male *vs*. Female	1.60 (1.37–1.87)	< 0.001	1.56 (1.27–1.91)	< 0.001	1.40 (1.13–1.73)	0.002	1.37 (1.11–1.69)	0.004
Diabetes (Yes/No)	–		0.93 (0.73–1.19)	0.581	0.85 (0.66–1.10)	0.221	0.85 (0.66–1.10)	0.211
TC, per mmol/L	–		1.14 (0.95–1.37)	0.151	1.13 (0.94–1.36)	0.181	1.12 (0.93–1.35)	0.224
TG, per mmol/L	–		0.99 (0.93–1.06)	0.735	1.00 (0.93–1.07)	0.886	1.00 (0.93–1.07)	0.971

LDL-C, per mmol/L	–	0.92 (0.75–1.14)	0.448	0.94 (0.76–1.16)	0.561	0.96 (0.77–1.19)	0.693
HDL-C, per mmol/L	–	0.78 (0.59–1.03)	0.077	0.80 (0.60–1.07)	0.126	0.81 (0.61–1.07)	0.140
SUA, per mg/dL	–	1.02 (0.96–1.08)	0.570	1.01 (0.95–1.08)	0.717	1.01 (0.95–1.07)	0.817
Current smoker (yes/no)	–	0.84 (0.70–1.00)	0.055	0.82 (0.68–0.99)	0.039	0.81 (0.67–0.98)	0.028
Current drinker (yes/no)	–	1.17 (0.94–1.44)	0.153	1.16 (0.93–1.44)	0.191	1.15 (0.93–1.44)	0.201
LAD, per cm	–	–		2.01 (1.62–2.49)	< 0.001	1.86 (1.48–2.33)	< 0.001
LVMI, per 10 g/m^2	–	–		–		1.05 (1.00–1.09)	0.044

Abbreviations as in Table 1.

Note: model 1: hypertension, BMI category, age, gender and race in the multivariate regression; model 2: additional variables including diabetes, plasma lipids, SUA, smoking, drinking, education, income, anti-arrhythmic medication, anti-hypertensive medication, mitral stenosis/regurgitation, and history of MI and HF; model 3: additional variable LAD; model 4: additional variable LVMI.

Figure legends

Figure 1. Gender-specific prevalence of interatrial block (IAB) by hypertension and body mass index (BMI) category.

Figure 2. Prevalence of interatrial block (IAB) for body mass index (BMI) category by hypertension.

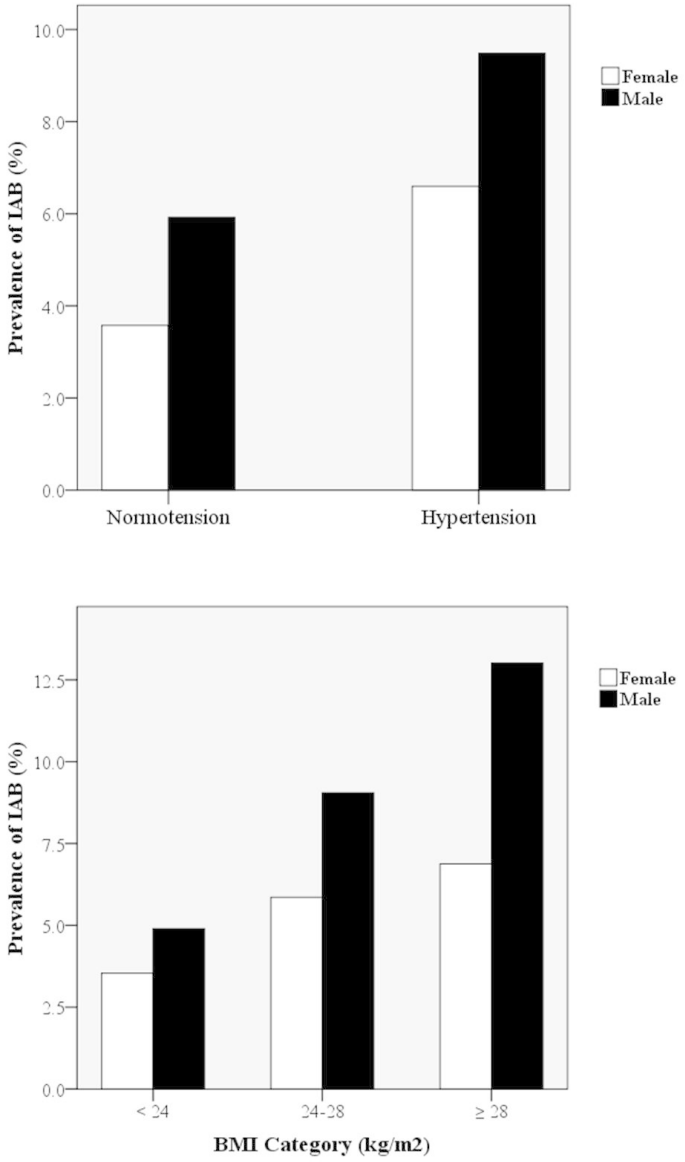

Figure 1. Gender-specific prevalence of interatrial block (IAB) by hypertension and body mass index (BMI) category.

170x273mm (150 x 150 DPI)

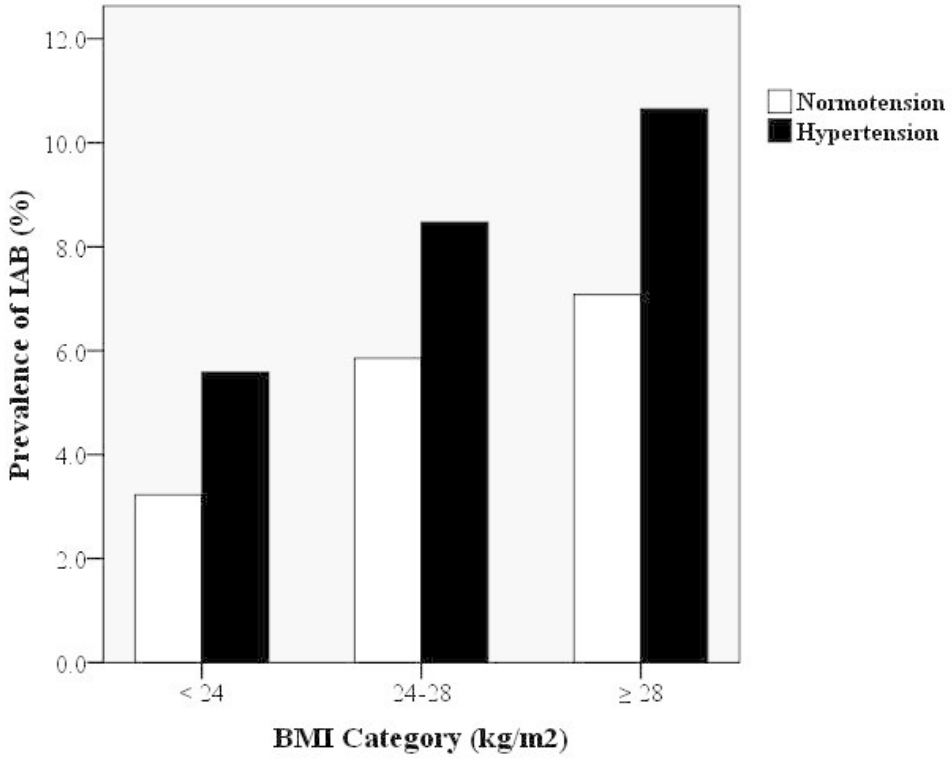

Figure 2. Prevalence of interatrial block (IAB) for body mass index (BMI) category by hypertension.

167x134mm (96 x 96 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-10
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, 11
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6, 11
		(b) Indicate number of participants with missing data for each variable of interest	-
Outcome data	15*	Report numbers of outcome events or summary measures	11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	7-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Independent associations of blood pressure and body mass index with interatrial block: A cross-sectional study in general Chinese population

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Independent associations of blood pressure and body mass index with interatrial block: A cross-sectional study in general Chinese population

Running Title: Blood pressure, body mass index and interatrial block

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Abstract

Objectives: This current study was performed to characterize the independent associations of obesity and hypertension with interatrial block (IAB) after adjusting for cardiovascular risk factors, echocardiographic left atrial diameter (LAD) and left ventricular mass index (LVMI) in a large general Chinese population.

Design: A cross-sectional study.

Setting and participants: A total of 11,956 permanent residents (≥ 35 years of age) from Liaoning Province in China were included in this study. Following the completion of a questionnaire, the enrolled participants were subjected to physical examinations, laboratory analyses, electrocardiogram (ECG) as well as echocardiogram. Linear and logistic regression analyses were performed to evaluate the associations of hypertension and obesity with IAB.

Outcome measures: IAB was defined as a prolongation of the P-wave duration ≥120 milliseconds on a digital 12-lead ECG.

Results: The prevalence of IAB in hypertensive individuals was higher than the normotensive in both men (9.5 *vs*. 5.9%; $P < 0.001$) and women (6.6 *vs*. 3.6%; $P < 0.001$). In addition, the prevalence of IAB exhibited a sharp increase with advancing BMI in both men (from 4.9 to 13.0%) and women (from 3.5 to 6.9%) (*P*s for trend < 0.001). Multiple relevant clinical covariates, echocardiographic LAD and LVMI were adjusted in the multivariate linear and logistic regression analyses. The results revealed that SBP, DBP and BMI were all

independently associated with P wave duration (β = 0.02, 0.09 and 0.25, respectively; all *P*s < 0.005). Furthermore, hypertension was found to be independently associated with IAB (OR = 1.27; *P* = 0.018), while both overweight and obesity exhibited higher odds of IAB (OR = 1.42 and 1.67, respectively; *P*s < 0.005), compared with BMI < 24.0 kg/m^2.

Conclusions: The key findings of this study highlighted that hypertension and overweight/obesity were independently and significantly associated with IAB in general Chinese population.

Key words: Interatrial block; Hypertension; Overweight/obesity.

Strengths and limitations of this study:

- The current study evaluated the independent associations of hypertension and overweight/obesity with IAB.
- This was a large population-based study, providing adequate data and sample size to delineate the study objective.
- Digital ECG was an important strength since automatic measures had superior validity and reliability compared to manual readings.
- Besides multiple clinical covariates, echocardiographic LAD and LVMI were also adjusted in multivariate logistic regression analyses.
- This was a cross-sectional study and further prospective ones should be conducted.

Introduction

Interatrial block (IAB) is characterized by the presence of a prolonged P-wave exceeding 120 ms on a 12-lead electrocardiogram (ECG) [1]. Accumulating reports have indicated that the prevalence of IAB is frequently underappreciated in clinical practice, particularly in the male and aging populations [2-4]. Further worsening the magnitude, IAB has been linked with numerous medical conditions including atrial arrhythmias [5-7], abnormal left atrial function [8], and thromboembolic ischemic stroke [9-12]. A follow-up study demonstrated that advancing P-wave durations are significantly associated with increasing cardiovascular and all-cause mortality [13]. Therefore, as a potentially crucial predictor of long-term patient outcome, additional efforts are necessitated in order to further elucidate the prevalence of IAB and its associated risk factors.

Obesity and hypertension are two highly prevalent conditions which remain to be burden on clinical resources, and remarkably, have been reported to possibly lead to left atrial enlargement. Previous studies have highlighted that both obesity and hypertension serve as risk factors for IAB, but the majority of these studies were performed in general hospitals with patients admitted for non-acute issues with limited sample sizes [14 15]. More notably, the study conducted by Atherosclerosis Risk in Communities (ARIC) demonstrated that both obesity and metabolic syndrome (especially with hypertension) are correlated with IAB, independent of age and other cardiovascular risk factors [16]. However, these studies failed to take left atrial size into account. Hence, the current study sought to examine whether these associations with IAB were

dependent on echocardiographic left atrial diameter (LAD) changes, a novel investigation that is yet to be conducted. In addition, no previous studies have incorporated large sample size studies emphasizing the risk factors contributing to IAB in Chinese population. Thereby, the current study aimed to assess the independent associations of obesity and hypertension with IAB after adjusting for cardiovascular risk factors and echocardiographic changes in general Chinese population using a large scale cross-sectional study.

Materials and methods

Study population

Between January 2013 and August 2013, a representative sample of men and women from Liaoning province of China were evaluated for cardiovascular risk factors (primarily hypertension) using a multi-stage, random, stratified, cluster-sampling scheme, referred to as the Northeast China Rural Cardiovascular Health Study (NCRCHS). The current study intentionally enrolled a representative sample aged ≥ 35 years, due to its purpose of evaluating hypertension and related cardiovascular risk factors. Within the Liaoning province, 3 counties (Dawa, Zhangwu, and Liaoyang) were selected from the eastern, southern, and northern regions, where the greater majority of residents are agricultural laborers. One township near a city in each county was randomly selected, totaling 3 townships, and 5-8 villages from each township were randomly selected, with a total of 18 rural villages finally selected. Those who were

pregnant, suffering from cancers or mental disorders were excluded from the current study.

All eligible permanent residents ≥35 years of age from each village (n = 14,016) were initially recruited, and a total of 11,956 (85.3%) participants completed the study. Subjects with incomplete data, poor ECG quality, atrial fibrillation/flutter, paced rhythm, WPW syndrome, or congenital heart diseases were excluded from the study, leaving a total of 11,264 participants for the final analyses. The current study was performed under the approval of the Ethics Committee of China Medical University in Shenyang, China. All the procedures were conducted in strict accordance with its ethical standards. All participants signed written consent after they had been informed of the study's objectives, benefits, medical procedures and confidentiality safeguards for personal information. Also, informed consent was obtained from the proxies of participants who were illiterate.

Data collection and measurements

Data were collected during a single clinic visit by cardiologists and trained nurses using a standard questionnaire with face-to-face interviews. All the potential investigators had received training in relation to the objectives of the study, how to perform the questionnaire, the standard methods of measurement, the importance of standardization, as well as the finer details of the study procedures. Only those who earned a perfect score on a post-training test were permitted to participate as study investigators. During the process of data collection, the investigators were provided with additional instructions and support. Data on demographic characteristics, medical history, and lifestyle risk factors were obtained using the abovementioned interviews

with a standardized questionnaire. A central steering committee with a subcommittee for quality control ensured that all data were collected in accordance with the aforementioned standards.

According to the guidelines of the American Heart Association, blood pressure (BP) was measured three times at 2-minute intervals, with a resting period of at least 5 minutes using a standardized automatic electronic sphygmomanometer (HEM-907; Omron, Kyoto, Japan). Independently, 2 doctors checked the calibration of the Omron device every month using a standard mercury sphygmomanometer in accordance with the British Hypertension Society protocol [17]. All participants were directed to avoid caffeinated beverages and exercise at least 30 min prior to evaluation. During BP measurement, the participants were seated with their arms supported at the level of their hearts. The mean value of three BP measurements were calculated and used in all the subsequent analyses. Hypertension was defined by the criteria widely employed and considered to be the worldwide standard in epidemiological research studies: a systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg and/or the use of antihypertensive medications. All participants were classified into the following groups based on mean SBP/DBP values and the most recent 2017 ACC/AHA guidelines [18]: (a) normal: SBP < 120 mmHg and DBP < 80 mmHg, (b) Elevated BP: SBP 120–129 mmHg and DBP < 80 mmHg, (c) Stage 1 hypertension: SBP 130–139 mmHg or DBP 80–89 mmHg, and (d) Stage 2 hypertension: SBP ≥ 140 mmHg or DBP ≥ 90 mmHg. During the course of the study, subjects who were taking anti-hypertensive medication and had a history of hypertension were considered to be at stage 2 hypertension as their BP levels would have

exceeded 140/90 mmHg during their initial hypertension diagnosis in accordance with the previous criteria. Weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, with all participants given lightweight clothing and evaluated barefoot. The body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). As recommended by the Working Group on Obesity in China, overweight was defined as a BMI of 24.0–27.9 kg/m^2, and obesity as a BMI of 28.0 kg/m^2 or higher [19].

Fasting blood samples were collected in the morning after ≥ 8 h of fasting. Blood samples were collected from the antecubital vein using BD Vacutainer tubes containing EDTA (Becton, Dickinson and Co., Franklin Lakes, NJ, USA). Subsequently, serum was isolated from whole blood, with all serum samples subsequently frozen at -20°C for testing at a central, certified laboratory. Fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), high density lipid cholesterol (HDL-C), low density lipid cholesterol (LDL-C), serum uric acid (SUA), and other routine blood biochemical indices were analyzed enzymatically using an auto-analyzer (Olympus AU640 Auto-Analyzer; Olympus Corp., Kobe, Japan). According to the criteria issued by World Health Organization, diabetes mellitus was defined as a FBG ≥ 7.0 mmol/L, and/or patients currently being treated for diabetes [20].

In addition, 12-lead resting, ten-second ECGs were performed on all participants by well-trained cardiologists using an electrocardiography machine (MAC 5500; GE Healthcare, Little Chalfont, Buckinghamshire, UK). The results were automatically analyzed by the MUSE Cardiology Information System (version 7.0.0; GE Healthcare). The P wave in each lead was

defined as the initial upward point or downward deflection from the isoelectric line to the point of the initial baseline. For the calculation of the P wave duration, onsets were defined as the earliest deflection in any lead, and offsets were defined as the latest deflection in any lead. Employing the most recent consensus guidelines [1], IAB was defined as a prolonged P-wave duration ≥120 milliseconds on a 12-lead ECG in the current study.

Echocardiograms were obtained using a commercially available Doppler echocardiograph (Vivid; GE Healthcare) with a 3.0-MHz transducer. Echocardiogram analyses and readings were performed by three separate doctors, all of whom were specialized in echocardiography, while two other specialists were called in case of any questions or uncertainties. LAD in the current study was defined as the left atrial anteroposterior measurement in the parasternal long-axis view according to the recommendations of the American Society of Echocardiography [21]. The reported LAD values in our study were not indexed by body surface area. Left ventricular mass index (LVMI) was calculated based on body surface area, while left ventricular hypertrophy (LVH) was defined as a LVMI > 115 g/m^2 in males and > 95 g/m^2 in females.

Statistical analysis

All statistical analyses were performed using SPSS 17.0 statistical software (SPSS, Inc., Chicago, IL, USA). Differences between groups were compared using a two-tailed Student's *t*-test for continuous variables and a χ^2 test for categorical variables. IAB prevalence by BMI category and hypertension were calculated and presented accordingly. Multivariate linear regression analyses were performed to identify the linear correlation between BP, BMI and P

wave duration. Multivariate logistic regression analyses were conducted to evaluate the link between hypertension and obesity with IAB. Data were expressed as odds ratio (OR) and 95% confidence interval (CI), β, mean ± standard deviation, or frequency and percentages; A *P* value < 0.05 was considered to be statistically significant.

Patient and public involvement

No patients were involved in setting the research questions or the outcome measures, nor were they involved in the design or performance of the study. No participants or patients were asked to advise on the interpretation or writing up of results. No plans were set in place to disseminate the results of the research to study participants.

Results

Characteristics of the study population

A total of 11,264 participants were included for final analyses, comprising of 5,126 men and 6,138 women with a mean age of 53.8 years. The general prevalence of IAB was calculated to be 6.3% (711/11,264) within the total population, which was significantly higher in subjects with left atrial enlargement (LAE) than those without (12.7 *vs*. 5.6%; $P < 0.001$). The subjects with IAB ($n = 711$) were significantly older and exhibited higher BMI, SBP, DBP, FBG, TC, TG, LDL-C, SUA, LAD, LVMI and heart rate values compared to those with normal P wave

durations (all *P*s < 0.005) (Table 1). Furthermore, the participants with IAB had significantly higher percentages of men, current drinker, anti-arrhythmic medication and anti-hypertensive medication, and higher prevalences of obesity, hypertension, diabetes mellitus, LAE and LVH (all *P*s < 0.05). Notably, HDL-C levels were found to be lower in subjects with IAB than those without IAB (*P* = 0.002). No significant differences were detected regarding smoking status between the two groups (*P* = 0.699). Furthermore, IAB participants were identified with a relatively higher prevalence of myocardial infarction (MI), heart failure (HF) and mitral stenosis/regurgitation, even though no statistical significance was detected (all *P*s > 0.05).

IAB prevalence by hypertension and BMI category

The gender-specific prevalence of IAB categorized according to hypertension and BMI category were shown in Figure 1. The prevalence of IAB in hypertensive subjects was found to be higher than the normotensive in both men (9.5 *vs*. 5.9%; *P* < 0.001) and women (6.6 *vs*. 3.6%; *P* < 0.001). In addition, the prevalence of IAB demonstrated a sharp rise with advancing BMI in both men (4.9, 9.0 and 13.0% in those with BMI < 24.0, 24.0–27.9 and ≥ 28.0 kg/m^2, respectively; *P* for trend < 0.001) and women (3.5, 5.9 and 6.9% in those with BMI < 24.0, 24.0–27.9 and ≥ 28.0 kg/m^2, respectively; *P* for trend < 0.001). The prevalence of IAB for BMI category by hypertension was calculated and presented in Figure 2. Our results demonstrated that the prevalence of IAB rose significantly with advancing BMI in both normotensive and hypertensive subjects (*P*s for trend < 0.001). Furthermore, higher prevalence of IAB was detected in the hypertensive subgroup at each BMI category (all *P*s < 0.05).

Linear relationship of BP, BMI with P wave duration

Multivariate linear regression analyses were performed to elucidate the association of BP, BMI and P wave duration, which are presented in Table 2. To better understand the complex effects of the numerous clinical factors associated with P wave duration, 4 sets of multivariate models were employed accordingly. In model 1, factors such as BP, BMI, age, gender and race were included, with results demonstrating that SBP, DBP and BMI were all independently associated with P wave duration ($\beta = 0.03$, 0.11 and 0.44, respectively; all Ps < 0.001). In model 2, additional variables such as FBG, plasma lipids, SUA, smoking, drinking, education, income, use of anti-arrhythmic medication, use of anti-hypertensive medication, mitral stenosis/regurgitation and history of MI and HF were adjusted accordingly, the results of which revealed that the independent associations were presented with a relatively lower β (all Ps $<$ 0.001). In model 3, after LAD had been further adjusted, the linear regression coefficients were found to decline to 0.02, 0.09 and 0.25 for SBP, DBP and BMI, respectively (all Ps < 0.001). Finally, in model 4, while LVMI was added to the multivariate linear regression, SBP, DBP and BMI were still all found to be independently associated with P wave duration (all Ps $<$ 0.005).

Associations between hypertension, overweight/obesity and IAB

In an attempt to further evaluate the associations of hypertension and overweight/obesity with IAB, we performed a series of multivariate logistic regression analyses, the results of which were shown in Table 3. In model 1, factors such as hypertension, BMI categories, age,

gender and race were included, with results demonstrating that hypertensive subjects exhibited higher odds of IAB than the normotensive subjects (OR = 1.42; 95%CI: 1.19–1.68). Compared with individuals with a BMI < 24.0 kg/m^2, higher odds of IAB were found in both overweight (OR = 1.76; 95%CI: 1.46–2.11) and obese individuals (OR = 2.32; 95%CI: 1.88–2.87). In model 2, additional variables of diabetes, plasma lipids, SUA, smoking, drinking, education, income, use of anti-arrhythmic medication, use of anti-hypertensive medication, mitral stenosis/regurgitation, history of MI and history of HF were adjusted accordingly, with the subsequent results obtained indicating that the independent associations preserved with relatively lower ORs (all *P*s < 0.05). In model 3, after LAD had been further adjusted, the ORs decreased to 1.29, 1.40 and 1.64 for hypertension, overweight and obesity, respectively (all *P*s < 0.05). Finally, LVMI was added in model 4, and the ORs changed to 1.27, 1.42 and 1.67 (all *P*s < 0.05).

Discussion

The current study aimed to conduct the largest evaluation (n = 11,264) of the potential factors associated with IAB in a general Chinese population. Our key findings indicated that IAB is significantly less prevalent in China compared to the American population. Our current study focused on obesity and hypertension, which are pandemic clinical issues that often coexist in people across the world. Our results identified a higher prevalence of IAB in subjects presenting with hypertension and advancing BMIs. Hypertension was further demonstrated to

increase the prevalence of IAB among overweight and obesity individuals. Furthermore, we uncovered that both obesity and hypertension were significantly and independently associated with IAB, even after adjusting for multiple clinical covariates, echocardiographic LAD and LVMI.

An extremely low prevalence of IAB was detected during the current study in comparison to previous data[2 4], which may be attributed to the fact that our study population comprised of rural residents with a relatively young mean age. In addition, it is also noteworthy that the prevalence of atrial fibrillation (AF) in Asian population is considerably lower compared to Western populations [22]. Based on the aforementioned analysis, we asserted that IAB might contribute to the relatively low prevalence of AF in China.

Some previous studies have reported the correlations of IAB with obesity [23 24] and hypertension [25-28]. Additionally, our results on the potential risk factors contributing to IAB are consistent with existing literatures reported in the ARIC [16] and Multiethnic Study of Atherosclerosis (MESA) studies [29]. The ARIC research demonstrated that IAB is significantly associated with obesity and hypertension in a cross-sectional population-based analysis, which are independent of age and cardiovascular risk factors [16]. This was consistent with our findings of the current study. The subgroup analysis of the MESA study further confirmed our discoveries, illustrating the association of increased BMI with IAB after adjusting for age, sex, ethnicity and pericardial fat [29]. However, the examination in both of these aforementioned two studies failed to adjust for factors such as LAD and LVMI. In contrast, a considerable strength

of our current study was our comprehensive adjustment for echocardiographic LAD and LVMI, in addition to cardiovascular risk factors in the multivariable analyses.

Our key findings revealed that the associations of hypertension and obesity with IAB were independent of echocardiographic LAD and LVMI, indicating that a prolonged P wave may occur prior to left atrial enlargement or at least was not consistent. The aforementioned finding was supported by Antoni Bayés de Luna's study, who proposed the concept of "Bayes' syndrome". He stated that the potential pathophysiology of IAB was directly related to a block in the area of the Bachmann's bundle. Although atrial enlargement and IAB share a similar electrocardiographic pattern, they are two separate entities [1 30 31]. Another study highlighted that the mechanism underlying the associations of hypertension and obesity with IAB is likely to be multifactorial in nature [32]. Obesity and hypertension have been demonstrated to increase cardiac preload, resulting in compensatory remodeling [33], with various reports indicating that obesity induces the expression of paracrine hormone with endovascular effects that may also alter atrial pressures and preload conditions [34 35]. The abovementioned findings elucidated the role of LAD in relation to the impact of obesity and hypertension on IAB. On the other hand, insulin resistance, a basic feature of metabolic syndrome, exhibits cellular and electrophysiologic effects by modifying metabolic function, including impairment of mitochondrial function and oxidative stress [36]. Furthermore, obesity has been reported to directly drive electrophysiologic remodeling by altering the myocardial matrix secondary to adipose-derived hormones [37 38]. Therefore, it can be summarized that the association of hypertension and obesity with IAB is

not entirely dependent on LAD and LVMI, which serves as an explanation for our findings regarding the independent influence of hypertension and obesity on IAB.

However, this study has several limitations. Firstly, the cross-sectional design of our study was unable to examine the longitudinal associations and distinguish causality between hypertension, obesity and IAB. Secondly, the detailed information of ECG waveform recorded using automatic measures were unable to be read by the MUSE system, so we did not differentiate between partial and advanced IAB. Thirdly, left atrial volume is a better index than LAD to estimate left atrial size according to the recommendations of the American Society of Echocardiography [21]. However, as a large-scale epidemiological investigation, we only measured LAD in our current study. Therefore, it may not represent an accurate picture of left atrial size although this measurement has been used extensively in clinical practice and research. Fourthly, the sample size in some subgroups by stage of hypertension in our study was relatively small. For example, the number of subjects with elevated BP stage and IAB was only 54, thus we didn't perform subgroup analyses according to BP stages. Finally, all the enrolled participants were from the same province in China, resulting in limited representation.

Conclusion

The current study evidenced a relatively higher prevalence of IAB in subjects with hypertension and advancing BMIs. Hypertension additionally augmented the prevalence of IAB

among individuals from each BMI category. Furthermore, it was uncovered that both hypertension and overweight/obesity significantly and independently increased the prevalence of IAB even after adjusting for multiple relevant covariates, echocardiographic LAD and LVMI.

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Authors' contributions GZS collected the data, analyzed and prepared the first draft of the manuscript. YZ supervised the data collection and reviewed the manuscript. NY coordinated the data collection. SJW did the data analyses. YXS conceived the study design, reviewed the final manuscript and serves as guarantor for the contents of this paper. All authors approved the final version.

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Table 1. Demographic characteristics of the study population

Variable		IAB - (*n* = 10,553)	IAB + (*n* = 711)	*P* value
Age, years		53.6 ± 10.6	55.5 ± 10.2	< 0.001
Male		4,724 (44.8)	402 (56.5)	< 0.001
Race of Han		10,009 (94.8)	668 (94.0)	0.300
Height, cm		160.4 ± 8.2	163.1 ± 8.1	< 0.001
Weight, kg		63.7 ± 11.3	69.2 ± 11.6	< 0.001
BMI, kg/m^2		24.7 ± 3.7	25.9 ± 3.6	< 0.001
BMI category, kg/m^2				< 0.001
	< 24	4,752 (45.0)	206 (29.0)	
	24–28	3,989 (37.8)	315 (44.3)	
	≥ 28	1,812 (17.2)	190 (26.7)	
SBP, mmHg		141.3 ± 23.3	149.4 ± 24.9	< 0.001
DBP, mmHg		81.7 ± 11.6	85.7 ± 12.7	< 0.001
Hypertension		5,288 (50.1)	459 (64.6)	< 0.001
BP category				< 0.001
	Normal	1,657 (15.7)	67 (9.4)	
	Elevated	1,333 (12.6)	54 (7.6)	

Variable	IAB - (*n* = 10,553)	IAB + (*n* = 711)	*P* value
Stage 1 Hypertension	2,275 (21.6)	131 (18.4)	
Stage 2 Hypertension	5,288 (50.1)	459 (64.6)	
FBG, mmol/L	5.88 ± 1.61	6.08 ± 1.75	0.003
Diabetes	1,067 (10.1)	89 (12.5)	0.041
TC, mmol/L	5.22 ± 1.07	5.37 ± 1.31	0.003
TG, mmol/L	1.62 ± 1.49	1.86 ± 1.65	< 0.001
LDL-C, mmol/L	2.92 ± 0.81	3.03 ± 0.93	0.001
HDL-C, mmol/L	1.41 ± 0.38	1.37 ± 0.38	0.002
SUA, mg/dL	4.87 ± 1.42	5.22 ± 1.45	< 0.001
Current smoker	3,712 (35.2)	245 (34.5)	0.699
Current drinker	2,313 (21.9)	196 (27.6)	< 0.001
Education level			0.004
≤ Primary school	5,274 (50.0)	348 (48.9)	
Middle school	4,328 (41.0)	273 (38.4)	
≥ High school	951 (9.0)	90 (12.7)	
Family income, CNY/y			0.281
≤ 5000	1,317 (12.5)	85 (12.0)	

Variable		IAB - (*n* = 10,553)	IAB + (*n* = 711)	*P* value
	5000-20000	5,787 (54.8)	373 (52.5)	
	> 20000	3,449 (32.7)	253 (35.6)	
LAD, mm		33.6 ± 3.9	35.3 ± 4.6	< 0.001
LAE		968 (9.4)	141 (20.4)	< 0.001
LVMI, g/m^2		81.7 ± 19.0	87.7 ± 21.5	< 0.001
LVH		1,047 (10.3)	111 (16.3)	< 0.001
P-wave duration, ms		99.4 ± 12.2	125.6 ± 7.7	< 0.001
Heart rate, bpm		71.5 ± 12.0	73.2 ± 15.5	0.004
Anti-arrhythmic medication		58 (0.5)	9 (1.3)	0.037
Anti-hypertensive medication		1,641 (15.6)	174 (24.5)	< 0.001
History of MI		117 (1.1)	13 (1.8)	0.082
History of HF		84 (0.8)	10 (1.4)	0.083
Mitral stenosis/regurgitation		158 (1.5)	17 (2.4)	0.062

Abbreviations: BMI = body mass index; BP = blood pressure; CNY = China Yuan; DBP = diastolic blood pressure; FBG = fasting blood glucose; HDL-C = high density lipid cholesterol; HF = heart failure; IAB = interatrial block; LAD = left atrial diameter; LAE = left atrial enlargement; LDL-C = low density lipid cholesterol; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; MI = myocardial infarction; SBP = systolic blood pressure; DBP = diastolic blood pressure; SUA = serum uric acid; TC = total cholesterol; TG =

triglycerides.

Note: data are expressed as mean ± standard deviation or *n* (%).

Table 2. Multivariate linear regression analyses for associations between BP, BMI and P-wave duration

	Model 1		Model 2		Model 3		Model 4	
	β	*P* value	β	*P* value	β	*P* value	β	*P* value
SBP, mmHg	0.03	< 0.001	0.03	< 0.001	0.02	< 0.001	0.02	0.002
DBP, mmHg	0.11	< 0.001	0.09	< 0.001	0.09	< 0.001	0.09	< 0.001
BMI, kg/m^2	0.44	< 0.001	0.36	< 0.001	0.25	< 0.001	0.25	< 0.001
Age, year	0.05	0.001	0.05	0.001	0.05	0.001	0.05	0.003
Male (1) *vs*. Female (0)	3.11	< 0.001	2.55	< 0.001	2.02	< 0.001	1.98	< 0.001
FBG, mmol/L	–		0.04	0.614	0.04	0.603	0.04	0.608
TC, mmol/L	–		0.83	0.007	0.73	0.018	0.71	0.023
TG, mmol/L	–		-0.05	0.682	-0.02	0.843	-0.02	0.899
LDL-C, mmol/L	–		-0.36	0.312	-0.21	0.573	-0.17	0.647

HDL-C, mmol/L	–	-1.96	< 0.001	-1.81	< 0.001	-1.81	< 0.001
SUA, mg/dL	–	0.05	0.646	0.01	0.914	0.00	0.994
Current smoker (yes/no)	–	0.02	0.949	0.13	0.663	0.10	0.751
Current drinker (yes/no)	–	1.21	0.001	1.19	0.002	1.18	0.002
Anti-arrhythmic medication (yes/no)	–	-1.83	0.263	-2.54	0.125	-2.60	0.116
Anti-hypertensive medication (yes/no)	–	1.25	0.001	1.17	0.003	1.15	0.003
Mitral stenosis/regurgitation (yes/no)	–	-0.04	0.968	-0.94	0.356	-1.12	0.273
History of MI (yes/no)	–	-0.16	0.891	-0.30	0.805	-0.33	0.785
History of HF (yes/no)	–	-1.40	0.314	-1.84	0.189	-1.89	0.179
LAD, cm	–	–		2.83	< 0.001	2.66	< 0.001
LVMI, g/m^2	–	–		–		0.01	0.208

Abbreviations as in Table 1.

Note: model 1: SBP, DBP, BMI, age, gender and race in the multivariate regression; model 2: additional variables including FBG, plasma lipids, SUA,

smoking, drinking, education, income, anti-arrhythmic medication, anti-hypertensive medication, mitral stenosis/regurgitation, and history of MI and HF; model 3: additional variable LAD; model 4: additional variable LVMI.

Table 3. Multivariate logistic regression analyses for associations between hypertension, BMI categories and IAB.

	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Hypertension (Yes/No)	1.42 (1.19–1.68)	< 0.001	1.32 (1.09–1.59)	0.004	1.29 (1.07–1.57)	0.009	1.27 (1.04–1.54)	0.018
BMI < 24 kg/m^2	1		1		1		1	
24–28	1.76 (1.46–2.11)	< 0.001	1.63 (1.35–1.98)	< 0.001	1.40 (1.15–1.72)	< 0.001	1.42 (1.16–1.74)	0.001
≥ 28	2.32 (1.88–2.87)	< 0.001	2.04 (1.62–2.57)	< 0.001	1.64 (1.28–2.10)	< 0.001	1.67 (1.30–2.14)	< 0.001
Age, per 10 years	1.14 (1.06–1.23)	0.001	1.16 (1.07–1.27)	< 0.001	1.14 (1.04–1.24)	0.005	1.12 (1.03–1.23)	0.010
Male *vs*. Female	1.60 (1.37–1.87)	< 0.001	1.56 (1.27–1.91)	< 0.001	1.40 (1.13–1.73)	0.002	1.37 (1.11–1.69)	0.004
Diabetes (Yes/No)	–		0.93 (0.73–1.19)	0.581	0.85 (0.66–1.10)	0.221	0.85 (0.66–1.10)	0.211
TC, per mmol/L	–		1.14 (0.95–1.37)	0.151	1.13 (0.94–1.36)	0.181	1.12 (0.93–1.35)	0.224
TG, per mmol/L	–		0.99 (0.93–1.06)	0.735	1.00 (0.93–1.07)	0.886	1.00 (0.93–1.07)	0.971

LDL-C, per mmol/L	–	0.92 (0.75–1.14)	0.448	0.94 (0.76–1.16)	0.561	0.96 (0.77–1.19)	0.693
HDL-C, per mmol/L	–	0.78 (0.59–1.03)	0.077	0.80 (0.60–1.07)	0.126	0.81 (0.61–1.07)	0.140
SUA, per mg/dL	–	1.02 (0.96–1.08)	0.570	1.01 (0.95–1.08)	0.717	1.01 (0.95–1.07)	0.817
Current smoker (yes/no)	–	0.84 (0.70–1.00)	0.055	0.82 (0.68–0.99)	0.039	0.81 (0.67–0.98)	0.028
Current drinker (yes/no)	–	1.17 (0.94–1.44)	0.153	1.16 (0.93–1.44)	0.191	1.15 (0.93–1.44)	0.201
Anti-arrhythmic medication (yes/no)	–	1.52 (0.73–3.16)	0.266	1.23 (0.57–2.68)	0.600	1.17 (0.53–2.56)	0.696
Anti-hypertensive medication (yes/no)	–	1.24 (1.00–1.52)	0.047	1.20 (0.97–1.48)	0.100	1.17 (0.94–1.45)	0.158
Mitral stenosis/regurgitation (yes/no)	–	1.48 (0.88–2.49)	0.141	1.10 (0.64–1.89)	0.723	1.04 (0.60–1.80)	0.898
History of MI (yes/no)	–	1.09 (0.60–2.00)	0.777	1.12 (0.61–2.06)	0.708	1.10 (0.60–2.02)	0.752
History of HF (yes/no)	–	1.36 (0.68–2.72)	0.386	1.29 (0.65–2.59)	0.467	1.26 (0.63–2.52)	0.521
LAD, per cm	–	–		2.01 (1.62–2.49)	< 0.001	1.86 (1.48–2.33)	< 0.001

LVMI, per 10 g/m^2	–	–	–	1.05 (1.00–1.09)	0.044

Abbreviations as in Table 1.

Note: model 1: hypertension, BMI category, age, gender and race in the multivariate regression; model 2: additional variables including diabetes, plasma lipids, SUA, smoking, drinking, education, income, anti-arrhythmic medication, anti-hypertensive medication, mitral stenosis/regurgitation, and history of MI and HF; model 3: additional variable LAD; model 4: additional variable LVMI.

Figure legends

Figure 1. Gender-specific prevalence of interatrial block (IAB) by hypertension and body mass index (BMI) category.

Figure 2. Prevalence of interatrial block (IAB) for body mass index (BMI) category by hypertension.

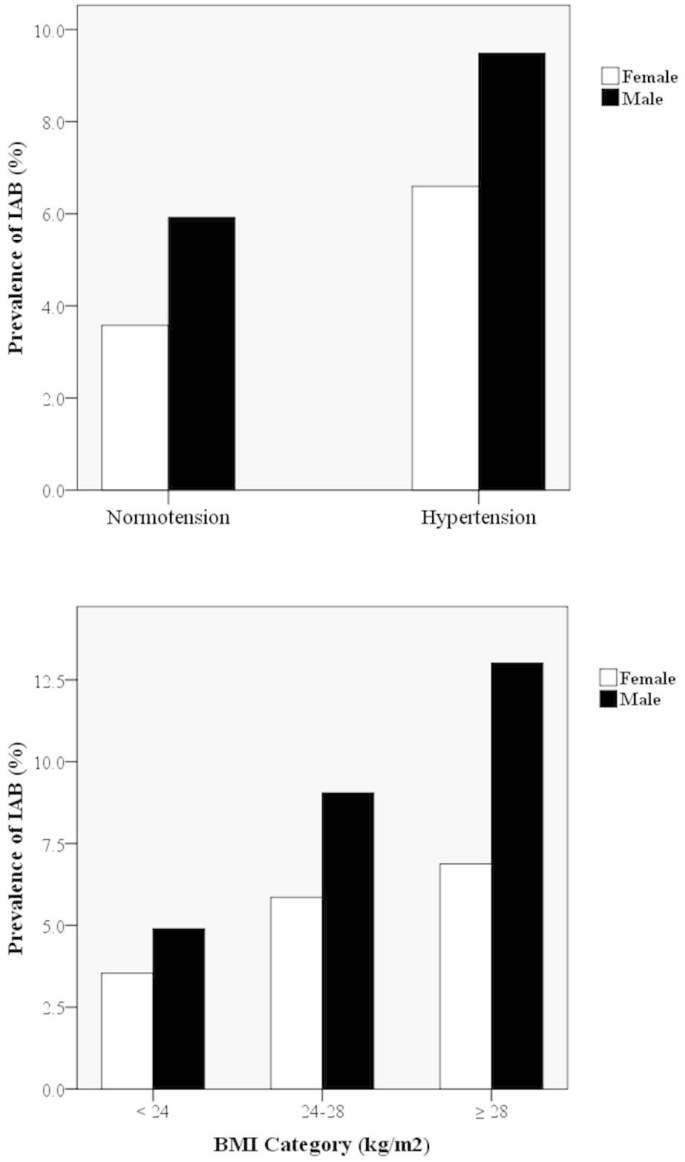

Figure 1. Gender-specific prevalence of interatrial block (IAB) by hypertension and body mass index (BMI) category.

170x273mm (150 x 150 DPI)

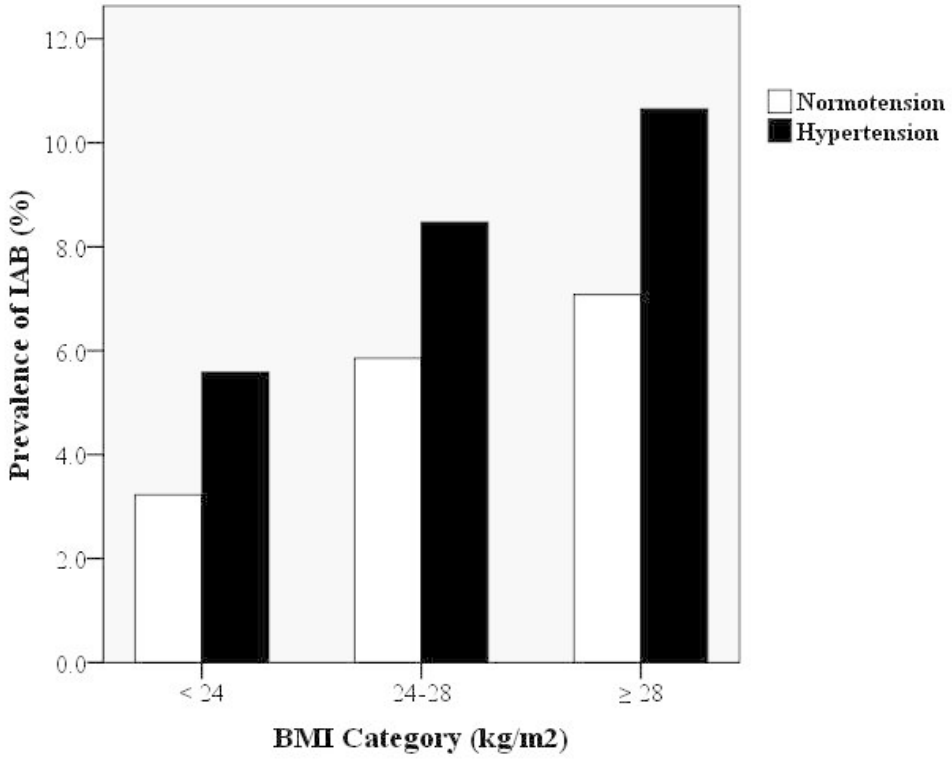

Figure 2. Prevalence of interatrial block (IAB) for body mass index (BMI) category by hypertension.

167x134mm (96 x 96 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-11
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-10
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11
		(*b*) Describe any methods used to examine subgroups and interactions	10-11
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, 11
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6, 11
		(b) Indicate number of participants with missing data for each variable of interest	-
Outcome data	15*	Report numbers of outcome events or summary measures	11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-14
		(*b*) Report category boundaries when continuous variables were categorized	7-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.