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ORIGINAL RESEARCH

Association Between Cumulative Body Mass Index Exposure and the Risk of Incident Cardiac Conduction Block

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BACKGROUND: The relationship between cumulative body mass index (cumBMI) exposure and cardiac conduction block (CCB) is not fully understood. This study aimed to explore the association between cumBMI and the risk of CCB.

METHODS AND RESULTS: A total of 107 860 participants of the Kailuan Study were included. Participants were then categorized into 4 groups based on their quartile of cumBMI. The association of cumBMI with CCB was estimated using the Cox proportional hazards regression model. During a median follow-up of 8.36 years, 1894 CCBs, 586 atrioventricular blocks (AVBs), 1273 intraventricular blocks, 851 right bundle branch blocks, and 319 any left bundle branch blocks occurred. After adjusting for potential confounders, the hazard ratios for CCB, atrioventricular block, intraventricular block, right bundle branch block, and any left bundle branch block were 1.86 (95% CI, 1.60–2.18), 2.51 (95% CI, 1.90–3.32), 1.55 (95% CI, 1.28–1.87), 2.14 (95% CI, 1.69–2.71), and 1.18 (95% CI, 0.81–1.72) for individuals in the highest quartile of cumBMI compared with those in the second quartile, respectively. Additionally, the subgroup analyses showed significant interactions between age, sex, and cumBMI for developing CCB (*P* for interaction<0.05).

CONCLUSIONS: Our findings suggest that higher cumulative BMI exposure significantly increased the risk of CCB, especially atrioventricular block. Monitoring cumulative BMI may help to identify high-risk CCB populations.

Key Words: cardiac conduction block ■ cumulative BMI ■ longitudinal study

Cardiac conduction block (CCB) is a common cardiovascular disease (CVD) in which damage to the cardiac conduction system results in electrophysiologic abnormalities that cause delayed or interrupted conduction of impulses within the atria or from the atria to the ventricles.[1] Patients with CCB may suffer from syncope and even sudden cardiac death in severe cases,[2,3] which seriously affects their survival and quality of life. Several population-based epidemiologic studies have found an increased risk of CVD and all-cause death in patients with prolonged PR interval and right bundle branch block (RBBB).[4–6] While pacemakers can be used to treat the end stage of CCB, pacemaker implantation may be associated with serious complications such as pneumothorax and infection.[7,8] Therefore, it is important to explore the risk factors of CCB for the primary prevention of CCB and to reduce the health and economic burden. The risk factors for CCB that have been established include hypertension, diabetes, and inflammatory response.[4,9–11]

Several studies have shown that obesity is associated with cardiac arrhythmias, which increases the

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CLINICAL PERSPECTIVE

What Is New?

- We found that cumulative body mass index (BMI) exposure increased the risk of cardiac conduction block (CCB) but was not associated with the development of any left bundle branch block.
- The risk associated with cumulative BMI exposure was found to be higher for both CCB and intraventricular block in individuals aged <45 years, and the risk of atrioventricular block was found to be higher in individuals aged ≥60 years when exposed to higher cumulative BMI; male participants exhibited a higher risk of CCB compared with female participants.

What Are the Clinical Implications?

- The findings of our study highlight the importance of individualized weight management for the prevention of CCB. Furthermore, maintaining a stable normal BMI level is helpful in controlling and reducing the incidence of CCB. Publicizing a normal BMI level for a long time is helpful to reduce the medical and socioeconomic burden of CCB in China.

Nonstandard Abbreviations and Acronyms

AVB	atrioventricular block
CARDIA	Coronary Artery Risk Development in Young Adults
CCB	cardiac conduction block
cumBMI	cumulative body mass index
IVB	intraventricular block

risks of sudden cardiac death and atrial fibrillation,[12–14] with potential mechanisms involving conduction abnormalities, infiltration of atrial musculature by contiguous epicardial fat, and increased atrial fibrosis.[15] Additionally, an animal study reported a significant increase in complex fractionated signals under conditions of sustained obesity, potentially resulting from conduction slowing caused by interstitial fibrosis or fat infiltration.[16]

Recent epidemiological studies have also reported that there is an association between obesity and an increased risk of CCB.[9,17] Those studies have mostly focused on single body mass index (BMI) measurements assessed at study baseline. However, the duration of exposure also plays a crucial role beyond BMI levels.[18,19] The CARDIA (Coronary Artery Risk Development in Young Adults) study proposed a method to quantify the risk burden brought by long-term exposure, using the sum of the product of cumulative levels and exposure time.[20] Cumulative exposure, as a composite measure of exposure level and duration, enables the identification of high-risk subgroups with greater specificity.[21,22] Furthermore, findings from the Framingham Heart Study have demonstrated that combining obesity and duration into a single construct provides stronger discriminatory power than a model relying solely on baseline BMI.[23] Few studies explored the relationship between cumulative BMI (cumBMI) and CCB. Therefore, we explored the relationship between cumBMI exposure and different types of CCB based on the Kailuan Study cohort (registration number: ChiCTR-TNC-11001489).

METHODS

Data Availability

The authors are responsible for the integrity and accuracy of the data analysis, and the relevant data are available from the corresponding author upon reasonable request.

Study Population

The Kailuan Study is a large, prospective, dynamic cohort study based on active and retired employees of the Kailuan community in Tangshan City, Hebei Province, China, in which demographic information, anthropometric parameters, and biochemical indexes were conducted biennially during June 2006 to December 2019 by trained staff according to a standardized uniform design. To observe the effect of cumBMI on CCB, we used those who joined the cohort for the first time and participated in at least 1 of the 2 consecutive physical examinations in 2006, 2008, 2010, and 2012 (eg, individuals who participated in the physical examination for the first time in 2006, and those who participated in either or both of the physical examinations in 2008 and 2010). Participants who were missing height, weight, and ECG data during the exposure period; those who had a history of CCB during the exposure period and were missing ECG data during follow-up; and those who attended the first physical examination but did not participate in 2 consecutive examinations (eg, individuals who participated in the first physical examination in 2006 and did not participate in either of the examinations in 2008 or 2010) were excluded. A total of 107 860 individuals were finally included. The flowchart of inclusion and exclusion of study participants is detailed in the Figure The study followed the Declaration of Helsinki and was approved by the Ethics Committee of Kailuan General Hospital. All participants gave written informed consent before study inclusion.

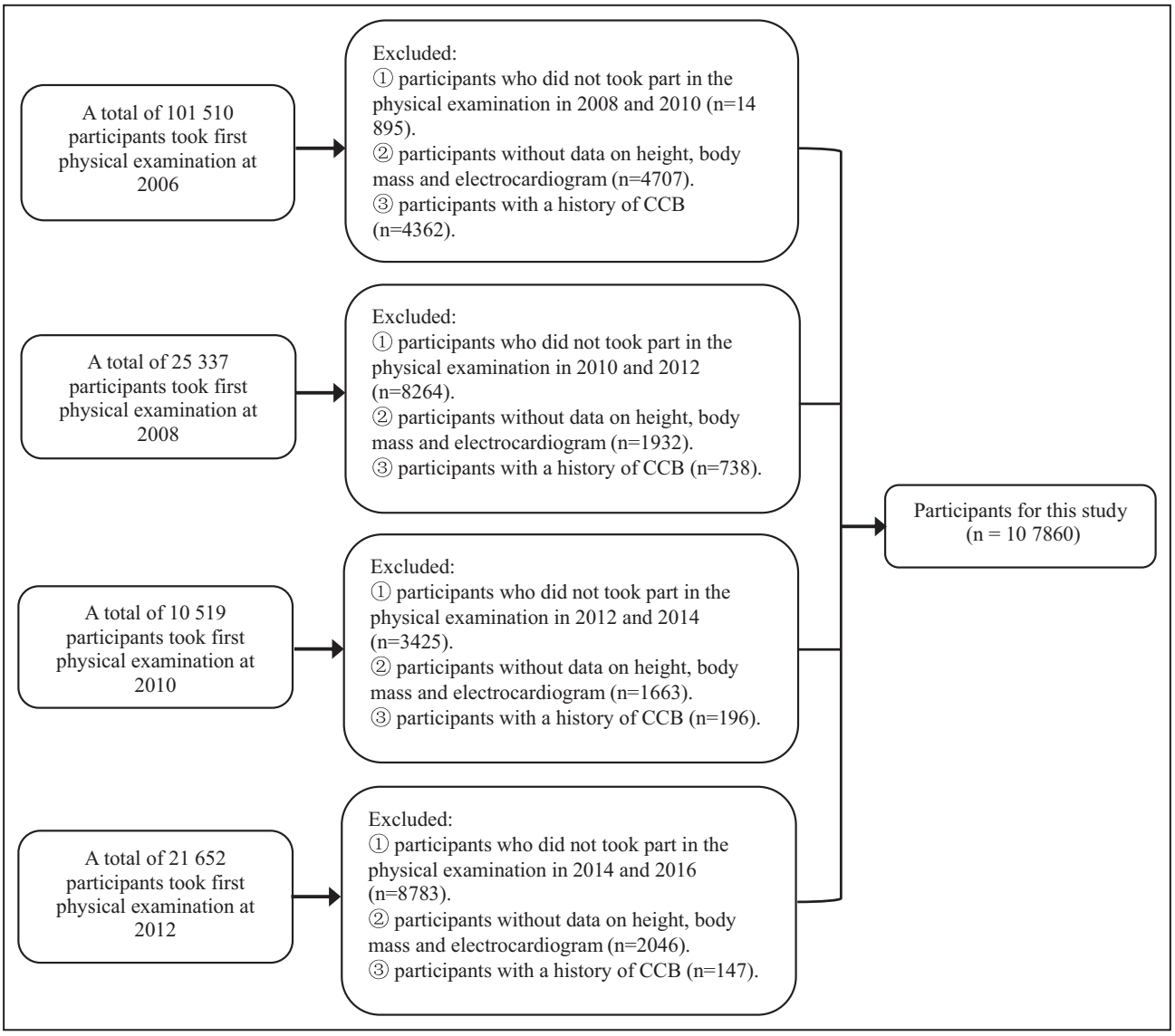

Figure. Flowchart of study participants.
CCB indicates cardiac conduction block.

Assessment of Exposure and Covariates

Epidemiological data were collected using a standardized, structured questionnaire by trained investigators and included demographic information (age, sex), lifestyle (smoking, alcohol consumption, physical activity, and salt intake), past medical history, and medication history. Smoking was defined as an average of at least 1 cigarette per day in the past year; alcohol consumption was defined as averaging at least 100 mL a day for more than a year; physical activity was defined as exercising for ≥30 minutes >3 times per week; and high salt intake was defined as >10 g/day of salt. Height, weight, and other relevant measurements were performed by trained health care professionals in strict accordance with a standardized protocol. Participants stood barefoot in lightweight clothing with arms relaxed according to the protocol, and standing height and weight were measured using a standardized instrument, with readings accurate to 1 decimal place.[24] BMI was calculated by dividing body mass (kg) by the square of height (m^2).

After fasting for 8 hours, 5 mL of elbow venous blood was drawn in the morning of the day of the physical examination to detect high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fasting blood glucose, and high-sensitivity C-reactive protein, all of which were detected by a fully automatic analyzer (Hitachi). The estimated glomerular filtration rate is calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.[25] Myocardial infarction and heart failure that occurred during follow-up were determined by trained medical personnel who

retrieved hospitalization data from their hospitals, according to the *International Classification of Diseases, Tenth Revision* (*ICD–10*) codes; hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or current use of antihypertensive medications; diabetes was defined as fasting blood glucose ≥7.0 mmol/L or self-reported use of hypoglycemic medication.

A 12-lead standard ECG examination was performed on the participants during the 2006 physical examination and biennially thereafter during follow-up. The 10-second 12-lead ECG examinations were collected from 7:00 to 9:00 AM after the participants had sufficiently rested quietly. ECG measurements and diagnosis were completed by at least 2 well-trained doctors. CCB events were diagnosed according to American College of Cardiology/American Heart Association/Heart Rhythm Society practice guidelines. Pacemaker status and the reasons for implantation were retrieved through the electronic medical record system. CCB was defined as the presence of any of the cardiac conduction disorders, including atrioventricular block (AVB [I–III]), pacemaker status due to AVB, complete RBBB, incomplete RBBB, complete left bundle branch block (LBBB), incomplete LBBB, left anterior branch block, left posterior branch block, and nonspecific intraventricular conduction block. AVB was defined as AVB I to III or pacemaker status due to AVB. Intraventricular block (IVB) was defined as nonspecific intraventricular conduction block, complete RBBB, incomplete RBBB, complete LBBB, incomplete LBBB, left anterior branch block, or left posterior branch block. RBBB was defined as complete RBBB or incomplete RBBB. Any LBBB was defined as complete LBBB, incomplete LBBB, left anterior branch block, or left posterior branch block. Diagnostic criteria are listed in more detail in Table S1.

Calculation and Grouping of Cumulative BMI

In our study, BMI at 3 different time points was defined as follows: the first physical examination was BMI1, the second physical examination was BMI2, and the third physical examination was BMI3. CumBMI was defined as the sum of the average BMI of the 2 examinations or the average BMI of the 3 examinations multiplied by the time interval between the 2 or 3 examinations, and was calculated as follows[26,27]:

$$\text{cumBMI} = \left[(\text{BMI1} + \text{BMI2})/2 \times \text{time}_{1-2}\right]$$

$$\text{cumBMI} = \left[(\text{BMI1} + \text{BMI3})/2 \times \text{time}_{1-3}\right]$$

$$\text{cumBMI} = \left[(\text{BMI1} + \text{BMI2})/2 \times \text{time}_{1-2}\right] + \left[(\text{BMI2} + \text{BMI3})/2 \times \text{time}_{2-3}\right]$$

where time_{1-2} represents the time interval between BMI1 and BMI2, time_{1-3} represents the time interval between BMI1 and BMI3, and time_{2-3} represents the time interval between BMI2 and BMI3. Calculation examples for cumBMI are presented in Figure S1. Grouping was based on the cumBMI quartiles: quartile 1, cumBMI <79.40; quartile 2, 79.40≤cumBMI <96.16; quartile 3, 96.16≤cumBMI <110.24; quartile 4, cumBMI ≥110.24.

Follow-Up and End Point Events

The time of the last physical examination was used as the starting point for follow-up. The outcome event of the study was new-onset CCB, including AVB, IVB, RBBB, and any LBBB, whichever occurred first. The outcome events of the secondary analyses include complete RBBB, incomplete RBBB, complete LBBB, incomplete LBBB, left anterior branch block, left posterior branch block, and nonspecific intraventricular conduction block. The time of the end point event was used as the end point time, while the date of the last physical examination was used as the end point time for those who did not have the end point event. Participants were followed up until CCB diagnosis; death; or December 31, 2019, whichever occurred first.

Statistical Analysis

Continuous variables with normal distribution were expressed as mean±SD and compared using 1-way ANOVA, while those with skewed distribution were presented as medians with interquartile ranges and compared by Kruskal–Wallis test. Categorical variables were expressed as frequencies and percentages and compared by χ^2 test. We used multiple imputation by chained equations to impute missing values for covariates. Participants were grouped by cumBMI quartile levels, and a Cox proportional hazards regression model was used to analyze the relationship between different levels of cumBMI and CCB. We constructed 2 models to adjust for potential confounding factors. Model 1 is a crude model; model 2 adjusted for age, sex, smoking, drinking, high salt intake, physical activity, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, high-sensitivity C-reactive protein, estimated glomerular filtration rate, hypertension, diabetes, myocardial infarction during the follow-up, heart failure during the follow-up, antidiabetic treatment, antihypertensive treatment, lipid-lowering drugs, and BMI single measurement. The covariates adjusted in model 2 were measured at the start of follow-up. The cumulative incidence of CCB in different cumBMI groups was calculated by the Kaplan–Meier method, and the log-rank test was used for comparison between groups. We used restricted cubic splines with 3 knots at the 25th, 50th, and 75th percentiles to

Table 1. Baseline Characteristics of Participants by cumBMI Quartile

Variables	Total (N=107 860)	Quartile 1 (N=26 965)	Quartile 2 (N=26 965)	Quartile 3 (N=26 965)	Quartile 4 (N=26 965)
Age, y	52.07±12.98	52.36±13.84	50.15±12.23	52.19±12.43	53.57±13.14
Male sex, n (%)	87 682 (81.3)	21 952 (81.4)	21 264 (78.9)	22 216 (82.4)	22 250 (82.5)
Current smoker, n (%)	32 596 (30.2)	8125 (30.1)	8949 (33.2)	8432 (31.3)	7090 (26.3)
Current drinker, n (%)	37 182 (34.5)	9761 (36.2)	9324 (34.6)	9282 (34.4)	8815 (32.7)
Physical activity, n (%)	14 422 (13.4)	4237 (15.7)	3174 (11.8)	3474 (12.9)	3537 (13.1)
High salt intake, n (%)	10 441 (9.68)	2800 (10.4)	2528 (9.38)	2585 (9.59)	2528 (9.38)
HDL-C, mmol/L	1.51±0.61	1.53±0.56	1.56±0.57	1.50±0.72	1.43±0.55
hs-CRP, mg/L	1.12 (0.50–2.50)	1.27 (0.60–2.70)	0.90 (0.40–2.08)	1.10 (0.50–2.38)	1.40 (0.64–2.90)
LDL-C, mmol/L	2.65±1.09	2.63±1.10	2.53±0.89	2.66±1.08	2.77±1.23
eGFR, mL/min per 1.73m^2	91.01±22.44	89.48±25.20	93.10±21.38	91.06±21.21	90.40±21.58
BMI at baseline, kg/m^2	25.25±3.41	23.39±3.47	23.37±2.36	25.48±2.44	27.95±3.18
CumBMI	93.00±26.14	56.84±14.27	88.72±4.68	102.92±4.02	123.53±11.65
Hypertension, n (%)	64 210 (59.5)	14 284 (53.0)	13 912 (51.6)	16 892 (62.6)	19 122 (70.9)
Diabetes, n (%)	22 358 (20.7)	4632 (17.2)	3984 (14.8)	5735 (21.3)	8007 (29.7)
Myocardial infarction during the follow-up, n (%)	1339 (1.24)	376 (1.39)	248 (0.92)	352 (1.31)	363 (1.35)
Heart failure during the follow-up, n (%)	2244 (2.08)	618 (2.29)	374 (1.39)	520 (1.93)	732 (2.71)
Antihypertension treatment, n (%)	31 005 (28.7)	5521 (20.5)	6653 (24.7)	8563 (31.8)	10 268 (38.1)
β blockers, n (%)	907 (0.84)	146 (0.54)	152 (0.56)	218 (0.81)	391 (1.45)
Non-dihydropyridine calcium channel blockers, n (%)	2209 (2.05)	383 (1.42)	331 (1.23)	534 (1.98)	961 (3.56)
Antidiabetic treatment, n (%)	6786 (6.29)	1271 (4.71)	1220 (4.52)	1843 (6.83)	2452 (9.09)
Lipid-lowering drug, n (%)	2582 (2.39)	381 (1.41)	467 (1.73)	693 (2.57)	1041 (3.86)

cumBMI indicates cumulative body mass index; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; and LDL-C, low-density lipoprotein cholesterol.

analyze the association between cumBMI and CCB. In addition, based on the model developed in this study, we used the C-statistic to predict the risk of CCB. With CCB as the dependent variable and cumBMI as the independent variable, the analysis was stratified by age and sex. To test the robustness of our findings, the following sensitivity analyses were performed: (1) To avoid possible reverse causality, we excluded participants who developed CCB within 2 years of follow-up; (2) to exclude the potential impact of cardiovascular events, we excluded participants who experienced myocardial infarction or heart failure during follow-up; (3) to avoid the impact of patients with weight loss on the results, we excluded participants who developed cancer or hepatic sclerosis during the exposure period; and (4) to avoid the influence of the differences in the duration between BMI measurements (different exposure periods) among different participants, we additionally adjusted for the duration between BMI measurements and also adopted the time-weighted cumulative BMI for analysis. All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC) and differences were considered statistically significant at $P<0.05$ (2-sided test).

RESULTS

Baseline Characteristics

A total of 107 860 participants were included in our study, of which 87 682 (81.3%) were men, and the mean age of the participants was 52.07±12.98 years. Grouping was done according to the cumBMI quartiles, and the mean cumBMI levels of the first to the fourth quartiles were 56.84±14.27, 88.72±4.68, 102.92±4.02, and 123.53±11.65, respectively. Baseline characteristics according to quartiles of cumBMI are presented in Table 1. The participants in the highest quartile group were older; were more likely to be men; were more likely to have higher levels of high-sensitivity C-reactive protein, low-density lipoprotein cholesterol, physical exercise and lower levels of high-density lipoprotein cholesterol and estimated glomerular filtration rate; were more likely to have a higher prevalence of hypertension, diabetes, heart failure, and myocardial infarction during follow-up; and were more likely to take antihypertensive, antidiabetic, and lipid-lowering agents.

After a median follow-up of 8.36 years, there were 1894 cases of CCB, 586 cases of AVB, 1273 cases of

IVB, 851 cases of RBBB, and 319 cases of any LBBB, and the incidence rate (per 1000 person-years) of CCB in the first through fourth quartile groups of the cumBMI were 2.27, 2.02, 2.55, and 3.11, respectively (Table 2). Cumulative incidence rates of CCB across cumBMI groups are presented in Figure S2.

Association of cumBMI With the Occurrence of CCB

When cumBMI was analyzed as a categorical variable (Table 2), the second quartile exhibited the lowest incidence rate of CCB (2.02 per 1000 person-years) compared with other cumBMI quartiles (2.27, 2.55, and 3.11 per 1000 person-years for the first, third, and fourth quartiles, respectively). The restricted cubic spline (RCS) plot and baseline data also support the use of the second quartile group as the reference group (Figure S3).

Using the second quartile of cumBMI as the referent category and adjusting for confounders, the multivariable adjusted hazard ratio (HR) for the occurrence of CCB , AVB , IVB , RBBB, and any LBBB in the fourth-quartile group were 1.86 (95% CI, 1.60–2.18), 2.51 (95% CI, 1.90–3.32), 1.55 (95% CI, 1.28–1.87), 2.14 (95% CI, 1.69–2.71), and 1.18 (95% CI, 0.81–1.72), respectively. With each 1 SD of cumBMI increasing, HR values for the occurrence of CCB, AVB, IVB, RBBB, and any LBBB were 1.52 (95% CI, 1.41–1.65), 1.90 (95% CI, 1.64–2.20), 1.37 (95% CI, 1.25–1.50), 1.56 (95% CI, 1.39–1.76), and 1.44 (95% CI, 1.19–1.75), respectively (Table 2).

In the secondary analyses, the HRs for complete RBBB and incomplete RBBB were 2.49 (95% CI, 1.66–3.74) and 2.84 (95% CI, 1.94–4.14), for individuals in the highest quartile of cumBMI compared with those in the second quartile, respectively (Table S2). There was no association between other subtypes of CCB and cumBMI.

Association of cumBMI With the Occurrence of CCB: Stratified by Sex and Age Separately

There was an interaction of cumBMI with age (*P* for interaction<0.05) and sex (*P* for interaction<0.05) for developing CCB (Table 3). The association between cumBMI and the risk of different types of CCB was further analyzed by age and sex stratification. Using the second quartile of cumBMI as the referent category, after correcting for the same confounders mentioned above, in participants aged <45 years, the fourth-quartile group had a higher risk of CCB (HR, 2.88 [95% CI, 1.99–4.17]) and IVB (HR, 2.98 [95% CI, 1.80–4.92]). Conversely, in participants aged ≥60 years, the fourth-quartile group had a higher risk of AVB (HR, 3.01 [95% CI, 1.80–5.02]). Men exhibited a higher risk of CCB (HR, 1.91 [95% CI, 1.62–2.25]) and AVB (HR, 2.60 [95% CI, 1.93–3.50]) compared with women in the fourth-quartile group.

Sensitivity Analyses

For the robustness of the findings, we excluded the participants who developed CCB within 2 years after the initiation of follow-up, those who experienced myocardial infarction or heart failure events during the follow-up period, and those who had cancer or liver cirrhosis during the exposure period (Tables S3 through S6). The association between cumBMI and the risk of CCB was consistent with the main results. Additionally, we adjusted for the duration between BMI measurements and also adopted the time-weighted cumBMI for analysis (Tables S7 and S8, Figure S4), and the results did not change significantly. We found that cumBMI has a moderate predictive value for CCB, with a C-statistic of 62.59%, indicating only fair discriminative ability (Table S9).

DISCUSSION

In this prospective cohort study, we found that cumBMI exposure increased the risk of CCB, particularly AVB. Furthermore, this association was altered by age and sex. However, we have not found an association between cumBMI exposure and any LBBB.

We found that cumBMI was a risk factor for CCB and that the risk of CCB increased with increasing cumBMI. The risk of CCB was increased by 35% and 86% in the third and fourth quartiles, respectively, compared with the second quartile of cumBMI. The higher HR observed for the fourth quartile compared with the second quartile highlights the cumulative burden of prolonged obesity on the cardiac conduction system, driven by mechanisms such as myocardial fibrosis, fatty infiltration, and increased epicardial fat.[15,16] The second quartile, representing moderate cumBMI exposure and the lowest observed risk, suggests that long-term maintenance of a normal BMI level is conducive to decreasing the risk of CCB. To our knowledge, this is the first prospective cohort study to investigate the association between cumBMI and CCB. A previous cross-sectional study reported that higher BMI (odds ratio, 1.26 per 5 kg/m^2 increase in BMI) was positively associated with the risk of AVB.[28] In addition, the CHS study also noted that higher BMI may increase the risk of CCB.[9] These studies support our findings to some extent. Compared with previous studies, our study calculated cumBMI through multiple repeated measurements of the data, taking into account both the cumulative and temporal effects of BMI, and thus yielded more reliable results, and our study is an

Table 2. Association of cumBMI With CCB

Outcomes	Quartile 1, HR (95% CI)	Quartile 2, HR (95% CI)	Quartile 3, HR (95% CI)	Quartile 4, HR (95% CI)	Per SD, HR (95% CI)
CCB					
Cases, n (%)	376 (1.39)	427 (1.58)	522 (1.94)	569 (2.11)	
Incidence rate (per 1000 person-years)	2.27	2.02	2.55	3.11	
Model 1	0.71 (0.61–0.83)	Reference	1.38 (1.21–1.57)	1.91 (1.68–2.16)	1.56 (1.48–1.65)
Model 2	0.88 (0.75–1.03)	Reference	1.35 (1.18–1.55)	1.86 (1.60–2.18)	1.52 (1.41–1.65)
AVB					
Cases, n (%)	112 (0.42)	132 (0.49)	152 (0.56)	190 (0.70)	
Incidence rate (per 1000 person-years)	0.68	0.62	0.74	1.02	
Model 1	0.63 (0.48–0.83)	Reference	1.34 (1.06–1.70)	2.24 (1.79–2.80)	1.78 (1.61–1.96)
Model 2	0.82 (0.61–1.09)	Reference	1.40 (1.10–1.80)	2.51 (1.90–3.32)	1.90 (1.64–2.20)
IVB					
Cases, n (%)	262 (0.97)	290 (1.08)	356 (1.32)	365 (1.35)	
Incidence rate (per 1000 person-years)	1.52	1.36	1.71	1.94	
Model 1	0.73 (0.61–0.88)	Reference	1.36 (1.17–1.59)	1.72 (1.47–2.01)	1.46 (1.37–1.56)
Model 2	0.89 (0.74–1.09)	Reference	1.28 (1.09–1.51)	1.55 (1.28–1.87)	1.37 (1.25–1.50)
RBBB					
Cases, n (%)	179 (0.66)	176 (0.65)	240 (0.89)	256 (0.95)	
Incidence rate (per 1000 person-years)	1.04	0.82	1.15	1.36	
Model 1	0.73 (0.58–0.92)	Reference	1.54 (1.27–1.88)	2.09 (1.72–2.54)	1.58 (1.46–1.72)
Model 2	0.90 (0.70–1.14)	Reference	1.53 (1.25–1.88)	2.14 (1.69–2.71)	1.56 (1.39–1.76)
Any LBBB					
Cases, n (%)	57 (0.21)	87 (0.32)	90 (0.33)	85 (0.32)	
Incidence rate (per 1000 person-years)	0.33	0.40	0.43	0.45	
Model 1	0.56 (0.39–0.81)	Reference	1.15 (0.85–1.54)	1.35 (1.00–1.82)	1.46 (1.28–1.67)
Model 2	0.66 (0.44–0.98)	Reference	1.07 (0.78–1.46)	1.18 (0.81–1.72)	1.44 (1.19–1.75)

Model 1: crude model. Model 2: adjusted for age, sex, smoking, drinking, high salt intake, physical activity, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, high-sensitivity C-reactive protein, estimated glomerular filtration rate, hypertension, diabetes, myocardial infarction during the follow-up, heart failure during the follow-up, antidiabetic treatment, antihypertensive treatment, lipid-lowering drug, and BMI single measurement. AVB indicates atrioventricular block; CCB, cardiac conduction block; cumBMI, body mass index; IVB, intraventricular block; LBBB, left bundle branch block; and RBBB, right bundle branch block.

important supplement and expansion to the field of CVD research.

In addition, we found that cumBMI exposure differentially impacted various types of CCB. Specifically, the risk of AVB escalated by 151% in the highest quartile of cumBMI group compared with the second-quartile group. The association between cumBMI exposure and AVB was more pronounced in comparison with IVB, aligning with findings from Liu et al.[17] Given the observational nature of our study, we are unable to analyze the underlying mechanisms. Some possible explanations are as follows: First, the atrioventricular node, being more susceptible to autonomic nerves, may experience an increased vagal tone that prolongs its refractory period, thereby delaying atrioventricular conduction; in contrast, the intraventricular conduction system, primarily influenced by sympathetic nerves, might be less affected by obesity.[29,30] Second, the atrioventricular node's conduction tends to be longer, while bundle branch conduction is more direct and rapid, making it less vulnerable to interference.[30,31] CumBMI exposure may be more likely to affect the conduction function of the atrioventricular node, thereby increasing the risk of AVB. In addition, we did not observe an association between cumBMI and any LBBB. Potential reasons might be that the right bundle branch, being thinner and longer than the left, is more prone to conduction blocks under the influence of adipocyte infiltration and inflammatory factors.[15] Moreover, in our study, the proportion of patients with hypertension taking drugs was ≈50%. The relatively high rate of medication adherence helps to better

Table 3. Subgroup Analyses for the Association of cumBMI With CCB

	Quartile 1, HR (95% CI)	Quartile 2, HR (95% CI)	Quartile 3, HR (95% CI)	Quartile 4, HR (95% CI)	*P* for interaction
CCB					<0.05
Age<45 y	0.85 (0.61–1.19)	Reference	1.45 (1.05–2.00)	2.88 (1.99–4.17)	
Age 45–60 y	0.74 (0.58–0.93)	Reference	1.40 (1.16–1.70)	1.82 (1.44–2.30)	
Age≥60 y	1.10 (0.83–1.46)	Reference	1.24 (0.98–1.56)	1.57 (1.21–2.03)	
					<0.05
Female sex	0.99 (0.66–1.48)	Reference	1.22 (0.83–1.79)	1.53 (0.99–2.38)	
Male sex	0.86 (0.72–1.03)	Reference	1.37 (1.18–1.58)	1.91 (1.62–2.25)	
AVB					0.09
Age <45 y	0.72 (0.44–1.18)	Reference	1.27 (0.78–2.07)	2.81 (1.62–4.87)	
Age 45–60 y	0.79 (0.51–1.22)	Reference	1.18 (0.81–1.73)	1.82 (1.16–2.86)	
Age ≥60 y	0.84 (0.46–1.56)	Reference	1.91 (1.19–3.07)	3.01 (1.80–5.02)	
					<0.05
Female sex	1.07 (0.56–2.06)	Reference	1.19 (0.61–2.34)	1.72 (0.78–3.77)	
Male sex	0.75 (0.54–1.03)	Reference	1.43 (1.09–1.86)	2.60 (1.93–3.50)	
IVB					<0.05
Age <45 y	0.99 (0.62–1.59)	Reference	1.61 (1.03–2.50)	2.98 (1.80–4.92)	
Age 45–60 y	0.74 (0.55–0.98)	Reference	1.42 (1.13–1.79)	1.64 (1.24–2.18)	
Age ≥60 y	1.13 (0.82–1.56)	Reference	1.02 (0.77–1.34)	1.20 (0.88–1.62)	
					0.14
Female sex	0.94 (0.56–1.59)	Reference	1.14 (0.70–1.84)	1.49 (0.87–2.54)	
Male sex	0.90 (0.73–1.11)	Reference	1.30 (1.09–1.55)	1.56 (1.27–1.91)	

Model adjusted for age, sex, smoking, drinking, high salt intake, physical activity, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, high-sensitivity C-reactive protein, estimated glomerular filtration rate, hypertension, diabetes, myocardial infarction during the follow-up, heart failure during the follow-up, antidiabetic treatment, antihypertensive treatment, lipid-lowering drug, and BMI single measurement. AVB indicates atrioventricular block; CCB, cardiac conduction block; cumBMI, body mass index; and IVB, intraventricular block.

control hypertension, thereby reducing the incidence of left ventricular remodeling.[32,33] Consequently, the incidence of any LBBB associated with it is relatively low, which may partially explain why statistical significance was not achieved in this subgroup.

In subgroup analyses, we found that the association between cumBMI exposure and CCB varied by age and sex. Specifically, the risk associated with cumBMI exposure was found to be higher for both CCB and IVB in individuals aged <45 years of age. This finding may be related to the impact of hypertension and diabetes on CVD. Some studies found that the risk of CVD in patients with type 2 diabetes, metabolic syndrome, and hypertension varies between age groups, and the association was more pronounced in the youth population.[34,35] In addition, obese young adults may have more obvious autonomic nervous system imbalances and increased sympathetic tone, which may increase cardiac electrophysiologic instability, leading to intraventricular block.[36–38] In contrast, the risk of AVB was found to be higher in individuals aged ≥60 years when exposed to higher cumBMI. This could be associated with age-related deterioration in atrioventricular node function among older adults. The decrease in the number of pacemaker cells in the sinoatrial node caused by aging is the main cause of impaired cardiac conduction function. The changes in the sinoatrial node caused by aging will further affect the atrioventricular node and atrioventricular bundle, increasing the risk of AVB in older adults.[39–42]

Moreover, we found that cumBMI exposure was associated with a higher risk of CCB in men compared with women. Villari et al found that, compared with men of the same age, premenopausal women had a lower degree of cardiac fibrosis, while men with CVD showed a higher degree of it.[43] Dworatzek et al attributed this difference to the protective effect of estrogen, demonstrating that estrogen can downregulate the expression of type I and type III collagen in cardiac fibroblasts.[44] Given that cardiac fibrosis is a pathological feature of CCB, these studies provide a potential biological explanation for the observed sex-related differences in CCB risk in our findings. Given these findings, it is crucial to focus on the heightened risk of IVB in younger individuals with obesity and AVB among their older counterparts. Additionally, men with obesity are at an elevated risk for CCB. These insights underscore the importance of tailored preventive and management strategies in addressing obesity-related CCB risks across different demographics.

The strength of our study is that we explored the association between cumBMI and CCB in a large prospective dynamic cohort study. Cumulative exposure was measured to reflect both exposure dose and exposure duration, circumventing potential regression dilution bias. Second, outcome events were identified by periodic ECGs rather than hospitalized diagnoses, which helped ensure that asymptomatic patients were also detected in a timely manner. However, there are some limitations to our study. First, our study did not collect information on pharmacologic treatment of obesity and bariatric surgery, yet pharmacologic or surgical treatment of obesity is conservative in China.[45] Second, we cannot conclude that causal effects regarding cumBMI and CCB were present in this observational study. Third, we did not observe the association between cumBMI and LBBB. In the future, it will be necessary to explore the relationship between cumBMI and the occurrence of LBBB in studies with larger sample sizes and longer follow-up periods. Fourth, while cumBMI alone demonstrates limited predictive ability, its key contribution is in identifying high-risk subgroups through the integration of exposure intensity and duration. More future studies should explore comprehensive models that combine cumBMI with other risk factors, such as inflammatory markers, to enhance predictive performance. Fifth, although BMI remains a widely used and practical metric for population-level obesity screening, it does not differentiate between fat mass and lean mass. Thus, future studies incorporating body composition measurements are warranted to refine obesity assessment. Finally, the population in this study was from a specific city in China, which may limit the generalizability of the findings.

CONCLUSIONS

In conclusion, our study found that cumBMI is a risk factor for CCB, especially AVB. Elevated cumBMI exposure is associated with an increased risk of CCB. Our findings emphasize that maintaining a stable normal BMI level is helpful to control and reduce the incidence of CCB.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S9
Figures S1–S4

REFERENCES

1. Smits JP, Veldkamp MW, Wilde AA. Mechanisms of inherited cardiac conduction disease. *Europace*. 2005;7:122–137. doi: 10.1016/j.eupc.2004.11.004
2. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, Fedorowski A, Furlan R, Kenny RA, Martín A, et al. 2018 ESC guidelines for the diagnosis and management of syncope. *Eur Heart J*. 2018;39:1883–1948. doi: 10.1093/eurheartj/ehy037
3. Kusumoto FM, Schoenfeld MH, Barrett C, Edgerton JR, Ellenbogen KA, Gold MR, Goldschlager NF, Hamilton RM, Joglar JA, Kim RJ, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Rhythm Society. *Circulation*. 2019;140:e382–e482. doi: 10.1161/cir.0000000000000628
4. Bussink BE, Holst AG, Jespersen L, Deckers JW, Jensen GB, Prescott E. Right bundle branch block: prevalence, risk factors, and outcome in the general population: results from the Copenhagen City heart study. *Eur Heart J*. 2013;34:138–146. doi: 10.1093/eurheartj/ehs291
5. Cheng S, Keyes MJ, Larson MG, McCabe EL, Newton-Cheh C, Levy D, Benjamin EJ, Vasan RS, Wang TJ. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. *JAMA*. 2009;301:2571–2577. doi: 10.1001/jama.2009.888
6. Haataja P, Anttila I, Nikus K, Eskola M, Huhtala H, Nieminen T, Jula A, Salomaa V, Reunanen A, Nieminen MS, et al. Prognostic implications of intraventricular conduction delays in a general population: the health 2000 survey. *Ann Med*. 2015;47:74–80. doi: 10.3109/07853890.2014.985704
7. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Rhythm Society. *Circulation*. 2018;138:e272–e391. doi: 10.1161/cir.0000000000000549
8. Kirkfeldt RE, Johansen JB, Nohr EA, Jørgensen OD, Nielsen JC. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. *Eur Heart J*. 2014;35:1186–1194. doi: 10.1093/eurheartj/eht511
9. Frimodt-Møller EK, Soliman EZ, Kizer JR, Vittinghoff E, Psaty BM, Biering-Sørensen T, Gottdiener JS, Marcus GM. Lifestyle habits associated with cardiac conduction disease. *Eur Heart J*. 2023;44:1058–1066. doi: 10.1093/eurheartj/ehac799
10. Nguyen MN, Kiriazis H, Gao XM, Du XJ. Cardiac fibrosis and arrhythmogenesis. *Compr Physiol*. 2017;7:1009–1049. doi: 10.1002/cphy.c160046

11. Zhao M, Gao J, Chen S, Yao S, Wang M, Wang C, Zhang S, Feng Z, Tian L, Li Y, et al. Association between new-onset type 2 diabetes and cardiac conduction diseases: a prospective cohort study. *J Am Heart Assoc*. 2023;12:e032237. doi: 10.1161/jaha.123.032237
12. Hookana E, Junttila MJ, Puurunen VP, Tikkanen JT, Kaikkonen KS, Kortelainen ML, Myerburg RJ, Huikuri HV. Causes of nonischemic sudden cardiac death in the current era. *Heart Rhythm*. 2011;8:1570–1575. doi: 10.1016/j.hrthm.2011.06.031
13. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham heart study. *Circulation*. 1983;67:968–977. doi: 10.1161/01.cir.67.5.968
14. Tedrow UB, Conen D, Ridker PM, Cook NR, Koplan BA, Manson JE, Buring JE, Albert CM. The long- and short-term impact of elevated body mass index on the risk of new atrial fibrillation the WHS (women's health study). *J Am Coll Cardiol*. 2010;55:2319–2327. doi: 10.1016/j.jacc.2010.02.029
15. Abel ED, Litwin SE, Sweeney G. Cardiac remodeling in obesity. *Physiol Rev*. 2008;88:389–419. doi: 10.1152/physrev.00017.2007
16. Mahajan R, Lau DH, Brooks AG, Shipp NJ, Manavis J, Wood JP, Finnie JW, Samuel CS, Royce SG, Twomey DJ, et al. Electrophysiological, electroanatomical, and structural remodeling of the atria as consequences of sustained obesity. *J Am Coll Cardiol*. 2015;66:1–11. doi: 10.1016/j.jacc.2015.04.058
17. Liu P, Wang Y, Zhang X, Zhang Z, Zhao N, Ou W, Wang G, Yang X, Li M, Zhang Y, et al. Obesity and cardiac conduction block disease in China. *JAMA Netw Open*. 2023;6:e2342831. doi: 10.1001/jamanetworkopen.2023.42831
18. Liu Y, Yan Y, Jiang T, Li S, Guo Y, Fernandez C, Barshop R, Bazzano L, He J, Chen W. Impact of long-term burden of body mass index and blood pressure from childhood on adult left ventricular structure and function. *J Am Heart Assoc*. 2020;9:e016405. doi: 10.1161/jaha.120.016405
19. Yan Y, Li S, Guo Y, Fernandez C, Bazzano L, He J, Mi J, Chen W. Life-course cumulative burden of body mass index and blood pressure on progression of left ventricular mass and geometry in midlife: the Bogalusa heart study. *Circ Res*. 2020;126:633–643. doi: 10.1161/circresaha.119.316045
20. Yano Y, Ning H, Allen N, Reis JP, Launer LJ, Liu K, Yaffe K, Greenland P, Lloyd-Jones DM. Long-term blood pressure variability throughout young adulth-ood and cognitive function in midlife: the coronary artery risk development in young adults (CARDIA) study. *Hypertension*. 2014;64:983–988. doi: 10.1161/hypertensionaha.114.03978
21. Domanski MJ, Tian X, Wu CO, Reis JP, Dey AK, Gu Y, Zhao L, Bae S, Liu K, Hasan AA, et al. Time course of LDL cholesterol exposure and cardiovascular disease event risk. *J Am Coll Cardiol*. 2020;76:1507–1516. doi: 10.1016/j.jacc.2020.07.059
22. Zhang Y, Pletcher MJ, Vittinghoff E, Clemons AM, Jacobs DR Jr, Allen NB, Alonso A, Bellows BK, Oelsner EC, Zeki Al Hazzouri A, et al. Association between cumulative low-density lipoprotein cholesterol exposure during young adulthood and middle age and risk of cardiovascular events. *JAMA Cardiol*. 2021;6:1406–1413. doi: 10.1001/jamacardio.2021.3508
23. Abdullah A, Wolfe R, Mannan H, Stoelwinder JU, Stevenson C, Peeters A. Epidemiologic merit of obese-years, the combination of degree and duration of obesity. *Am J Epidemiol*. 2012;176:99–107. doi: 10.1093/aje/kwr522
24. Jia Z, Zhou Y, Liu X, Wang Y, Zhao X, Wang Y, Liang W, Wu S. Comparison of different anthropometric measures as predictors of diabetes incidence in a Chinese population. *Diabetes Res Clin Pract*. 2011;92:265–271. doi: 10.1016/j.diabres.2011.01.021
25. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF III, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612. doi: 10.7326/0003-4819-150-9-200905050-00006
26. Zemaitis P, Liu K, Jacobs DR Jr, Cushman M, Durazo-Arvizu R, Shoham D, Palmas W, Cooper R, Kramer H. Cumulative systolic BP and changes in urine albumin-to-creatinine ratios in nondiabetic participants of the multi-ethnic study of atherosclerosis. *Clin J Am Soc Nephrol*. 2014;9:1922–1929. doi: 10.2215/cjn.02450314
27. Liu P, Li J, Yang L, Zhang Z, Zhao H, Zhao N, Ou W, Zhang Y, Chen S, Wang G, et al. Association between cumulative uric acid to high-density lipoprotein cholesterol ratio and the incidence and progression of chronic kidney disease. *Front Endocrinol (Lausanne)*. 2023;14:1269580. doi: 10.3389/fendo.2023.1269580
28. Shan R, Ning Y, Ma Y, Liu S, Wu J, Fan X, Lv J, Wang B, Li S, Li L. Prevalence and risk factors of atrioventricular block among 15 million chinese health examination participants in 2018: a nation-wide cross-sectional study. *BMC Cardiovasc Disord*. 2021;21:289. doi: 10.1186/s12872-021-02105-3
29. Manolis AA, Manolis TA, Apostolopoulos EJ, Apostolaki NE, Melita H, Manolis AS. The role of the autonomic nervous system in cardiac arrhythmias: the neuro-cardiac axis, more foe than friend? *Trends Cardiovasc Med*. 2021;31:290–302. doi: 10.1016/j.tcm.2020.04.011
30. Prystowsky EN, Gilge JL. Atrioventricular conduction: physiology and autonomic influences. *Cardiol Clin*. 2023;41:293–306. doi: 10.1016/j.ccl.2023.03.015
31. Ren L, Wu JC. Novel insight into atrioventricular node conduction. *Cell Res*. 2024;34:539–540. doi: 10.1038/s41422-024-00996-3
32. Fung MJ, Thomas L, Leung DY. Left ventricular function and contractile reserve in patients with hypertension. *Eur Heart J Cardiovasc Imaging*. 2018;19:1253–1259. doi: 10.1093/ehjci/jex338
33. Tadic M, Cuspidi C, Marwick TH. Phenotyping the hypertensive heart. *Eur Heart J*. 2022;43:3794–3810. doi: 10.1093/eurheartj/ehac393
34. Wang C, Yuan Y, Zheng M, Pan A, Wang M, Zhao M, Li Y, Yao S, Chen S, Wu S, et al. Association of age of onset of hypertension with cardiovascular diseases and mortality. *J Am Coll Cardiol*. 2020;75:2921–2930. doi: 10.1016/j.jacc.2020.04.038
35. Zhao M, Song L, Sun L, Wang M, Wang C, Yao S, Li Y, Yun C, Zhang S, Sun Y, et al. Associations of type 2 diabetes onset age with cardiovascular disease and mortality: the Kailuan study. *Diabetes Care*. 2021;44:1426–1432. doi: 10.2337/dc20-2375
36. Bonnemeier H, Richardt G, Potratz J, Wiegand UK, Brandes A, Kluge N, Katus HA. Circadian profile of cardiac autonomic nervous modulation in healthy subjects: differing effects of aging and gender on heart rate variability. *J Cardiovasc Electrophysiol*. 2003;14:791–799. doi: 10.1046/j.1540-8167.2003.03078.x
37. Grassi G, Seravalle G, Colombo M, Bolla G, Cattaneo BM, Cavagnini F, Mancia G. Body weight reduction, sympathetic nerve traffic, and arterial baroreflex in obese normotensive humans. *Circulation*. 1998;97:2037–2042. doi: 10.1161/01.cir.97.20.2037
38. Koenig J, Jarczok MN, Warth M, Ellis RJ, Bach C, Hillecke TK, Thayer JF. Body mass index is related to autonomic nervous system activity as measured by heart rate variability--a replication using short term measurements. *J Nutr Health Aging*. 2014;18:300–302. doi: 10.1007/s12603-014-0022-6
39. Dobrzynski H, Boyett MR, Anderson RH. New insights into pacemaker activity: promoting understanding of sick sinus syndrome. *Circulation*. 2007;115:1921–1932. doi: 10.1161/circulationaha.106.616011
40. Jones SA. Ageing to arrhythmias: conundrums of connections in the ageing heart. *J Pharm Pharmacol*. 2006;58:1571–1576. doi: 10.1211/jpp.58.12.0002
41. Kistler PM, Sanders P, Fynn SP, Stevenson IH, Spence SJ, Vohra JK, Sparks PB, Kalman JM. Electrophysiologic and electroanatomic changes in the human atrium associated with age. *J Am Coll Cardiol*. 2004;44:109–116. doi: 10.1016/j.jacc.2004.03.044
42. Monfredi O, Boyett MR. Sick sinus syndrome and atrial fibrillation in older persons-a view from the sinoatrial nodal myocyte. *J Mol Cell Cardiol*. 2015;83:88–100. doi: 10.1016/j.yjmcc.2015.02.003
43. Villari B, Campbell SE, Schneider J, Vassalli G, Chiariello M, Hess OM. Sex-dependent differences in left ventricular function and structure in chronic pressure overload. *Eur Heart J*. 1995;16:1410–1419. doi: 10.1093/oxfordjournals.eurheartj.a060749
44. Dworatzek E, Mahmoodzadeh S, Schriever C, Kusumoto K, Kramer L, Santos G, Fliegner D, Leung YK, Ho SM, Zimmermann WH, et al. Sex-specific regulation of collagen I and III expression by 17β-estradiol in cardiac fibroblasts: role of estrogen receptors. *Cardiovasc Res*. 2019;115:315–327. doi: 10.1093/cvr/cvy185
45. Zeng Q, Li N, Pan XF, Chen L, Pan A. Clinical management and treatment ofobesity in China. *Lancet Diabetes Endocrinol*. 2021;9:393–405. doi: 10.1016/s2213-8587(21)00047-4