Effect of visit-to-visit blood pressure variability on cardiovascular events in populations with different body mass indexes: a prospective cohort study

Haojia Chen,1,2 Youren Chen,1,2 Weiqiang Wu,3 Jianhuan Huang,2,3 Zekai Chen,2,3 Zhichao Chen,3 Xizhuo Yan,4 Shouling Wu5

ABSTRACT

Objective This study was performed to explore the effects of visit-to-visit blood pressure variability (BPV) on cardiovascular events (CVEs) in people with various body mass indexes (BMIs).

Design Prospective cohort study.

Setting The average real variability of systolic blood pressure (ARVSBP) was the indicator for visit-to-visit BPV. The participants were divided into three groups: normal weight, overweight and obesity. We further divided these groups into four subgroups based on the ARVSBP. A Cox regression model was used to calculate the HRs of the ARVSBP on CVEs in the same and different BMI groups. Additionally, a competitive risk model was used to calculate the HRs of the ARVSBP on CVEs in the same BMI group.

Participants In total, 41,043 individuals met the inclusion criteria (no historical CVEs or tumours, no incidence of CVEs or tumours and no death during the four examinations) and had complete systolic blood pressure and BMI data.

Results A total of 868 CVEs occurred. The cumulative incidence of CVEs increased as ARVSBP rose in both the normal weight and overweight groups. In same BMI groups, the risk of CVEs significantly increased as ARVSBP increased only in the normal weight group (highest quintiles of ARVSBP: HR (95% CI) 2.20 (1.46–3.31)). In the different BMI groups, the risk of CVEs in the ARVSBP subgroup in each BMI group was higher than that of the least quintile of ARVSBP in the normal weight group (highest quintiles of ARVSBP in obesity: HR (95% CI) 2.28 (1.47–3.55)). The result of the competitive risk model did not change.

Conclusions As BMI and ARVSBP increase, the risk of CVEs increases. However, the risk of visit-to-visit BPV on CVEs varies in different BMI groups, especially in people of normal weight.

Trial registration number CHICTR-TNC1100 1489.

INTRODUCTION

During the past 30 years, the incidence of overweight or obesity has doubled worldwide. The situation of overweight or obesity is more severe in China, where the incidence has increased by two to three times.1,2 The body mass index (BMI) is a convenient indicator that is widely used in research of overweight or obesity. Previous studies have shown that the BMI is closely related to visit-to-visit blood pressure variability (BPV). Li et al3 found that the visit-to-visit BPV increased by 0.029 units with every 1-unit increase in the BMI. Our previous study4 showed that the average real variability of systolic blood pressure (ARVSBP) increased by 0.077 units with every 1-unit increase in the BMI. Another previous study5 showed that the relationship between the BMI and ARVSBP may involve the release of inflammatory factors by adipose tissue, resulting in higher arterial stiffness and thus higher BPV.

Cardiovascular events (CVEs) are one of the main causes of death, and approximately 18 million people worldwide die of CVEs annually.6 Previous studies have shown that a high BMI and increased visit-to-visit BPV are risk factors for CVEs.7–9 A meta-analysis showed that for each 5 kg/m2 increase in the BMI, the risk of coronary heart disease and...
stroke increased by 1.27 and 1.18 times, respectively. Another meta-analysis showed that the risk of stroke increased by 1.15 times, coronary heart disease by 1.10 times and CVEs by 1.18 times as the visit-to-visit BPV of systolic blood pressure (SBP) increases.

A higher BMI and higher visit-to-visit BPV are associated with a higher risk of CVEs. To the best of our knowledge, however, no studies have focused on the effect of visit-to-visit BPV on CVEs in different BMI groups. The Kailuan Study was a community-based study on the assessment and intervention of risk factors for CVEs. The participants in that study underwent physical examinations every 2 years beginning in 2006, including measurement of blood pressure (BP), height and weight. Annual checks and information on CVEs and death were also recorded. In the present study, we examined the effect of visit-to-visit BPV on CVEs in different BMI groups using the Kailuan Study cohort.

PARTICIPANTS AND METHODS

Patient and public involvement
Patients and the public were not involved in the design of this study.

Study participants
This prospective cohort study began in 2006–2007. Staff members from Kailuan Corporation in China who were working in or retired from the Kailuan Group participated in this study. All staff members were >18 years of age and were from geographical locations throughout China. Most of the participants were from the northeast area of China (Beijing, Hebei and so on). Therefore, this study has certain guiding significance for the prevention of CVEs among North China’s population. Participants with complete SBP and BMI data obtained at the first medical examination and with no history of CVEs or tumours were included. Medical doctors were in charge of the first to fourth medical examinations, which were performed every 2 years. We excluded individuals with any missing data on SBP or the incidence of CVEs, tumours or death during the period in which the four medical examinations were performed.

Data collection
Details of the epidemiological investigations and anthropometry index measurements were previously reported. Questionnaires were personally administered by the research doctors to collect information on the participants’ sociodemographic status (sex, age, education, economic status), lifestyle habits (alcohol consumption, smoking status, physical exercise) and personal health history (hypertension, diabetes, CVEs). Smoking was defined as having smoked an average of at least one cigarette per day during the past year. Drinking was defined as an average daily alcohol consumption of more than 100 mL (alcohol concentration of >50% v/v) during the past 1 year and lasting for more than 1 year.

Physical exercise was defined as engaging in exercise at least three times weekly for more than 30 min each time. The information about historical CVEs was through querying and/or searching inpatient diagnoses and endpoint records of the participants.

BP measurements were performed as follows. The participants were strictly prohibited from drinking alcohol, drinking coffee, or smoking for at least 30 min. BP was measured after they had sat quietly for 15 min. Each participant stretched out his or her bare right upper arm at 45° and ensured that the elbow lay on the surface of the desk at the level of the heart. Suitable cuffs were wound around the participant’s upper arm and tightened close to the skin with proper tension. The cuff size varied by the upper arm circumference as follows: 12×22 cm cuff for a 22 to 26 cm arm circumference, 16×30 cm cuff for 27 to 34 cm circumference, 16×36 cm cuff for 35 to 44 cm circumference and 16×42 cm cuff for 45 to 52 cm circumference. The upper edge of the cuff was positioned approximately 2.5 cm above the chelidon, and the centre was positioned immediately above the brachial artery. An adjusted mercury sphygmomanometer was used during the first four physical examinations to measure the BP of the right brachial artery. Phase 1 Korotkoff sounds were chosen for the SBP reading, and phase 5 Korotkoff sounds were chosen for the diastolic BP reading. An electronic sphygmomanometer (HEM-8102A; Omron, Daling, China) was used to measure the BP of the right brachial artery during the fifth physical examination. The average of three BP readings obtained three times at 1 min intervals was recorded as the final BP of each participant for each physical examination.

For height and weight measurements (accurate to 0.1 cm and 0.1 kg, respectively), the participants stood barefoot in thin garments and no hat, and their height and weight were measured using a calibrated RGZ-120 scale from 7:30 AM to 9:00 AM. The BMI was calculated as weight divided by height squared (kg/m²).

Biochemical measurements
Blood samples were taken from the antecubital vein of the participants after an overnight fast and collected in EDTA tubes. The serum supernatant was measured within 4 hours. The hexokinase method was used to measure the fasting blood glucose concentration. The total cholesterol and high-density lipoprotein concentrations were enzymatically measured (Mind Bioengineering, Shanghai, China). A high-sensitivity nephelometric assay (Cias Latex CRP-H; Kanto Chemical, Tokyo, Japan) was used to measure the high-sensitivity C reactive protein concentration. All biochemical parameters were measured with an automatic biochemical analyzer (Hitachi 747; Hitachi, Tokyo, Japan).

Relevant definitions
Measurement of visit-to-visit BPV includes the SD of BP, the coefficient of variation, the variability uncorrelated with mean BP and the average real variability.
There has been uncertainty on which indicator to adopt for BPV. Previous studies mostly used SD of BP.\textsuperscript{14} However, SD was not able to distinguish systematic changes in BP over time from true variation in BP.\textsuperscript{15,16} Some studies pointed out that the root-mean-square error can better show the authenticity of BPV. However, this indicator was not statistically significant to the incidence but the mortality of CVEs.\textsuperscript{13} And the subjects of most studies were elderly. Meanwhile, some studies hold different points of view that the average real variability can more effectively predict the damage to the target organ and requires no time sequence of BP readings.\textsuperscript{17-20} In addition, previous studies on the correlation between visit-to-visit BPV and BMI only have the indicator of average real variability. As the result of the above, average real variability was chosen as the indicator for visit-to-visit BPV in this study. The formula\textsuperscript{18-20} for calculating $\text{ARV}_{\text{SBP}}$ was as follows: $\text{ARV}_{\text{SBP}} = (|\text{sbp}_2 - \text{sbp}_1| + |\text{sbp}_3 - \text{sbp}_2| + |\text{sbp}_4 - \text{sbp}_3|)/3$, where sbp1, sbp2, sbp3 and sbp4 represent SBP of the first to fourth physical examinations, respectively. Previous studies have illustrated that systolic BPV can more effectively predict CVEs than diastolic BPV.\textsuperscript{21,22} Thus, we focused on systolic BPV rather than diastolic BPV in this study. For participants undergoing antihypertensive therapy, 10 mm Hg was added to the SBP and 5 mm Hg was added to the diastolic BP.\textsuperscript{23,24}

**Outcomes**

The 2012 medical examination was considered the start of the follow-up period, and the last follow-up date was 31 December 2016; this was the last date on which new CVEs and death were recorded. CVEs included stroke (haemorrhagic stroke and ischaemic stroke) and myocardial infarction. Every year, trained doctors referred to the inpatient diagnoses and endpoint records of the patients in the hospitals that were affiliated with the Kailuan Group and the municipal Medicare-appointed hospitals. All diagnoses were confirmed by professional physicians on the basis of the inpatient medical records. The incidence of death was also obtained from provincial population statistics offices or medical records of medical insurance companies annually. The diagnosis standard of stroke and myocardial infarction was based on the guidelines issued by the American Heart Association and European
Society of Cardiology, and the diagnosis standard varied according to the updates of the guidelines.

**Statistical methods**

We calculated the interaction between the BMI grouping variables and the ARVSBP grouping variables (p for interaction <0.05). Therefore, a stratified analysis by BMI was used for ARVSBP in this study. According to the criteria for defining obesity in China, the participants' body weight was divided into three groups by the BMI as follows: 25 normal weight (BMI of <24.0 kg/m²), overweight (BMI of ≥24 to<28.0 kg/m²) and obesity (BMI of ≥28.0 kg/m²). Because there was no normal range of ARVSBP and it had a skewed distribution, ARVSBP of each BMI group was divided into four quartiles (Q1, Q2, Q3 and Q4) (figure 1). SAS 9.4 (SAS Institute, Cary, North Carolina, USA) was used for the data analysis. Continuous variables are presented as mean±SD, and we used single-factor variance analysis for comparison of groups. Categorical variables are presented as number and percentage, and the χ² test was used for comparison of groups. The Kaplan-Meier method was used to calculate the cumulative incidence of CVEs in all subgroups. The log-rank test was used to determine whether a significant difference was present in the incidence of CVEs in different groups within the same BMI group. A Cox proportional hazard regression model was used to assess the risk of CVEs in relation to ARVSBP in the same and different BMI groups. We used a competitive risk model for a second risk assessment of CVEs in relation to ARVSBP in different BMI groups, taking into account the effect of death in the Cox risk model. A sensitivity analysis was used to separately analyse patients with hypertension (SBP of >140 mm Hg

---

**Table 1** General information of the study population

| Group | BMIC<24.0 | 24.0≤BMI<28.0 | BMIG>28.0 | Total (n=41043) | Corresponding tests | P trend |
|-------|-----------|---------------|-----------|-----------------|--------------------|---------|
| Man, % | 11489 (70.8) | 13749 (79.9) | 5993 (78.9) | 31231 (76.1) | F test | <0.0001 |
| Age, year | 46.8±11.9 | 48.5±10.9 | 44.7±12.9 | 47.6±11.4 | F test | <0.0001 |
| SBP1, mm Hg | 122±18.5 | 130±20.0 | 136±20.6 | 128±20.2 | F test | <0.0001 |
| SBP2, mm Hg | 124±18.9 | 131±19.5 | 137±20.2 | 129±20.0 | F test | <0.0001 |
| SBP3, mm Hg | 125±18.6 | 133±19.1 | 137±19.5 | 131±20.0 | F test | <0.0001 |
| SBP4, mm Hg | 126±19.1 | 133±19.3 | 137±19.3 | 131±19.7 | F test | <0.0001 |
| ARVSBP, mm Hg | 10.8 (9.09) | 11.3 (9.34) | 12.0 (9.32) | 11.2 (9.34) | F test | <0.0001 |
| Smoking, % | 4925 (30.3) | 5241 (30.4) | 2138 (28.1) | 12304 (30.0) | χ² test | 0.001 |
| Drinking, % | 2762 (17.0) | 3122 (18.1) | 1158 (15.2) | 7042 (17.2) | χ² test | <0.0001 |
| Snorer, % | 1396 (8.6) | 2316 (13.5) | 1486 (19.6) | 5198 (12.7) | χ² test | <0.0001 |
| Salt intake, % | 1486 (9.2) | 1813 (10.5) | 891 (11.7) | 4190 (10.2) | χ² test | <0.0001 |
| Physical exercise, % | 2043 (12.6) | 2287 (13.3) | 1006 (13.2) | 5336 (13.0) | χ² test | 0.133 |
| HDL | 1.60±0.40 | 1.53±0.39 | 1.50±0.38 | 1.55±0.39 | F test | <0.0001 |
| TC, mmol/L | 4.81±1.08 | 4.96±1.20 | 5.00±1.15 | 4.91±1.14 | F test | <0.0001 |
| Heart rate, beat/min | 73.4±10.3 | 73.3±9.62 | 74.0±9.64 | 73.5±9.90 | F test | <0.0001 |
| Hypertension, % | 4023 (24.8) | 7043 (40.9) | 4114 (54.2) | 15180 (37.0) | χ² test | <0.0001 |
| Antihypertensive therapy, % | 635 (3.9) | 1496 (8.7) | 1006 (13.2) | 3137 (7.6) | χ² test | <0.0001 |
| Diabetes mellitus, % | 742 (4.6) | 1444 (8.4) | 839 (11.0) | 3025 (7.4) | χ² test | <0.0001 |
| hs-CRP, log | −0.29±0.72 | −0.11±0.65 | 0.05±0.60 | −0.15±0.68 | F test | <0.0001 |

**Table 2** Cumulative incidence of CVEs in the ARVSBP subgroups within the same BMI group

| Group | Total | Q1 | Q2 | Q3 | Q4 | Log-rank |
|-------|-------|----|----|----|----|---------|
| BMIC<24.0 | No. of case (%) | 273 (1.68) | 30 (0.73) | 54 (1.34) | 69 (1.70) | 120 (2.96) | <0.001 |
| 24.0≤BMI<28.0 | No. of case (%) | 387 (2.25) | 68 (1.60) | 85 (1.95) | 89 (2.04) | 145 (3.41) | <0.001 |
| BMIC≥28 | No. of case (%) | 208 (2.74) | 41 (2.16) | 39 (2.04) | 55 (2.92) | 73 (3.84) | 0.001 |

**Corresponding tests**

F test

**P trend**

<0.0001

---

ARVSBP, average real variability of systolic blood pressure; BMI, body mass index; HDL, high-density lipopr otein; hs-CRP, high-sensitivity C reactive protein; sbp1, sbp2, sbp3 and sbp4, systolic blood pressure of the first to fourth physical examinations; TC, total cholesterol.

---

Chen H, et al. BMJ Open 2020;10:e035836. doi:10.1136/bmjopen-2019-035836
or diastolic BP of >90 mm Hg or receiving antihypertensive therapy) and those with antihypertensive therapy in the four medical examinations because of the potential influence of hypertension and antihypertensive therapy on CVEs and BPV.26 27 A two-sided p<0.05 was considered statistically significant.

RESULTS

A total of 59008 participants underwent the first physical examination, of whom 41043 were included in the final analysis after exclusion for the following reasons. We excluded 3330 participants with previous CVEs, 330 with a history of tumours, and 1439 with incomplete or missing data regarding height or weight in the first physical examination. Among the remaining 53909 participants, we further excluded 5941 with incidence of CVEs, 2248 with a tumour and 2259 who died during the four examinations. We also excluded 2418 with any missing SBP data. Among the final participants, 31231 (76.1%) were men and their mean age was 47.6±11.4 years. The mean follow-up time was 3.75±0.54 years.

Participants’ general information

Increases in BMI were associated with increases in the mean or proportion of the total cholesterol level, salt intake, diabetes mellitus, hypertension, antihypertensive therapy, snoring, SBP of the four examinations, ARVSBP and high-sensitivity C reactive protein level (p<0.05). The overweight group had the highest rates of older age, male sex, smoking, physical exercise and drinking (table 1).

Cumulative incidence of CVEs in relation to visit-to-visit BPV in different BMI groups

During the mean follow-up of 3.75±0.54 years, 868 CVEs occurred. As the BMI increased, the cumulative incidence of CVEs gradually but significantly increased (p<0.05). In the normal weight and overweight groups, as the ARVSBP increased, the cumulative incidence of CVEs gradually increased (p<0.05). The cumulative incidence of CVEs gradually increased from Q2 to Q4 in the obesity group (p<0.05). Except for Q4, the cumulative incidence of CVEs significantly increased as the BMI increased within the same ARVSBP subgroup (p<0.05) (table 2).

Cox proportional hazard regression model for risk assessment of CVEs in relation to visit-to-visit BPV in BMI groups

The incidence of CVEs was the dependent variable, ARVSBP was the independent variable and Q1 of the normal weight group served as the control group (p for interaction <0.05). After adjusting for confounding factors, the risk of CVEs in the ARVSBP subgroups within each BMI group was higher than that in Q1 of ARVSBP in the normal weight group (p<0.05). The risk of Q4 in the obesity group was the highest at 2.28 times. In the overweight and obesity groups, however, the HR did not seem to vary substantially as the ARVSBP increased (figure 1).

| Group | ARVSBP | No. of cases | Person-years | Model 1 HR (95% CI) | Model 2 HR (95% CI) | Competitive risk model HR (95% CI) |
|-------|--------|--------------|--------------|---------------------|---------------------|-----------------------------------|
| BMI<24.0 | Q1 | 30 | 15653 | 1 (Reference) | 1 (Reference) | 1 (Reference) |
|       | Q2 | 54 | 15246 | 1.64 (1.05 to 2.56) | 1.62 (1.03 to 2.53) | 1.60 (1.02 to 2.50) |
|       | Q3 | 69 | 15164 | 1.89 (1.23 to 2.91) | 1.77 (1.15 to 2.72) | 1.73 (1.12 to 2.68) |
|       | Q4 | 120 | 14766 | 2.88 (1.92 to 4.33) | 2.20 (1.46 to 3.31) | 2.10 (1.37 to 3.22) |
| P trend | – | – | – | <0.001 | <0.001 | – |
| 24.0≤BMI>28.0 | Q1 | 68 | 16279 | 1 (Reference) | 1 (Reference) | 1 (Reference) |
|       | Q2 | 85 | 16505 | 1.13 (0.82 to 1.56) | 1.06 (0.77 to 1.47) | 1.06 (0.76 to 1.46) |
|       | Q3 | 89 | 16352 | 1.11 (0.81 to 1.52) | 0.98 (0.70 to 1.34) | 0.97 (0.70 to 1.35) |
|       | Q4 | 145 | 15579 | 1.65 (1.23 to 2.22) | 1.18 (0.86 to 1.61) | 1.17 (0.85 to 1.61) |
| P trend | – | – | – | 0.001 | 0.36 | – |
| BMI≥28.0 | Q1 | 41 | 7279 | 1 (Reference) | 1 (Reference) | 1 (Reference) |
|       | Q2 | 39 | 7256 | 0.89 (0.57 to 1.38) | 0.84 (0.54 to 1.32) | 0.84 (0.54 to 1.32) |
|       | Q3 | 55 | 7043 | 1.23 (0.82 to 1.85) | 1.12 (0.74 to 1.70) | 1.12 (0.73 to 1.70) |
|       | Q4 | 73 | 6970 | 1.47 (0.99 to 2.17) | 1.17 (0.78 to 1.77) | 1.17 (0.76 to 1.80) |
| P trend | – | – | – | 0.015 | 0.23 | – |

Model 1: adjusted for age and sex; Model 2 and Competition model: adjusted for sex, age, total cholesterol level, heart rate, high-sensitivity C reactive protein, high-density lipoprotein level, sbp1, smoking, salt intake, drinking, exercise and diabetes mellitus.

ARVSBP, average real variability of systolic blood pressure; BMI, body mass index; CVEs, cardiovascular events; sbp1, systolic blood pressure of the first physical examination.

Table 3 Risk assessment of CVEs in relation to ARVSBP in the same BMI groups
The incidence of CVEs was the dependent variable, ARV$_{SBP}$ was the independent variable, and the Q1 group of ARV$_{SBP}$ served as the reference group in the same BMI group (p for interaction <0.05). After adjusting for confounding factors, as ARV$_{SBP}$ increased, the risk of CVEs showed an increasing trend in the normal weight group (p<0.05), and the risk in the Q4 group was 2.20 times that in the Q1 group. In the overweight and obesity groups, there was no significant risk of CVEs with an increase in ARV$_{SBP}$ (table 3).

In total, 961 deaths occurred during the follow-up period. The incidence of CVEs was the dependent variable, ARV$_{SBP}$ was the independent variable, and the Q1 group of ARV$_{SBP}$ in each BMI group served as the reference group. The effect of ARV$_{SBP}$ on CVEs in the same BMI group remained unchanged. However, the risk was slightly lower than that in the previous Cox model (table 3).

**Sensitivity analysis**

Participants undergoing hypertensive and antihypertensive therapy were excluded, and a sensitivity analysis was then performed after adjusting for confounding factors. In the normal weight group, the risk of CVEs in Q3 and Q4 was still higher than that in Q1, although the risk was slightly lower than that in all participants. However, Q2 was not significant. This risk also tended to increase as ARV$_{SBP}$ increased. However, the results had no statistical significance in the overweight and obesity groups (table 4).

### DISCUSSION

This study is the first to show that compared with the Q1 group of ARV$_{SBP}$ in the normal weight group, the risk of CVEs significantly increased as the BMI and ARV$_{SBP}$ increased. However, there were comparatively few variations in the overweight and obesity groups. In addition, we found that visit-to-visit BPV has different effects on CVEs in different BMI groups. The risk of CVEs increased with increasing ARV$_{SBP}$ only in the normal weight group.

We found that the risk of CVEs in relation to ARV$_{SBP}$ in each BMI group was significantly higher than that in Q1 of the normal weight group with an increase in BMI and ARV$_{SBP}$. This finding indicates that in different BMI groups, the risk of CVEs increased as ARV$_{SBP}$ rose. However, there was no obvious change in the gradient, which indicated the significance of the ARV$_{SBP}$ subgroups in various BMI groups. This finding also suggests that prediction of the risk of CVEs using ARV$_{SBP}$ mainly depended on the BMI and that the predictive value of ARV$_{SBP}$ was higher in the lower-weight groups. Furthermore, a higher BMI was associated with a greater effect of ARV$_{SBP}$ on the risk of CVEs. The reason for these findings may be that the BMI and ARV$_{SBP}$ were risk factors for CVEs, and the interaction...
(as a protective factor) between the BMI and ARV\textsubscript{SBP} reduced the effect of ARV\textsubscript{SBP} on CVEs.

We found that the incidence of CVEs increased as the ARV\textsubscript{SBP} increased in the normal and overweight groups. However, the risk of CVEs caused by an increase in ARV\textsubscript{SBP} was meaningful only in the normal weight group (among the subgroups of ARV\textsubscript{SBP}, in the normal weight group, the risk of CVEs of Q4 was increased 2.20 times compared with Q1). Our results compensate for the lack of previous studies. Previous cohort studies and meta-analyses\textsuperscript{6-8} showed that visit-to-visit BPV was a risk factor for CVEs, but they did not consider BMI and ARV\textsubscript{SBP} as risk factors or the interaction between them. Our previous study also showed that ARV\textsubscript{SBP} increased as the BMI increased; Visit-to-visit BPV was also a risk factor for CVEs.\textsuperscript{4,8}

Why an increased risk of CVEs was related to an increase in ARV\textsubscript{SBP} only in the normal weight group is unclear. The mechanism of this finding remains to be investigated, but we consider that the effect of smoking cannot be ignored. A previous study showed that smokers have a low BMI and high BPV.\textsuperscript{29-30} After adjusting for smoking in our study, ARV\textsubscript{SBP} was still a risk factor in the normal weight group, which supports the conclusion of this study. Additionally, in the overweight and obesity groups, a high BMI was a risk factor for CVEs, together with a higher level or proportion of risk factors such as SBP, cholesterol and diabetes mellitus. These findings weaken the predictive meaning of ARV\textsubscript{SBP} in the risk of CVEs. Another important point is that participants in the normal weight group tended to be younger and have a lower incidence of BP therapy. However, participants with a higher BMI were more likely to be older and hypertensive and to be undergoing BP therapy.

Because of the effect of death on the Cox risk model, we chose a competitive risk model analysis to re-estimate the effect of ARV\textsubscript{SBP} on CVEs in the same BMI group. We found that the effect of ARV\textsubscript{SBP} in the same BMI group on CVEs did not change; however, the risk was slightly lower than that in the original Cox model. The competitive risk model more realistically reflected the effect of ARV\textsubscript{SBP} on CVEs in the same BMI group on CVEs, and the effect of ARV\textsubscript{SBP} on CVEs in the same BMI group remained significant. Considering the possibility that hypertension and antihypertensive therapy may affect the results of our study, a sensitivity analysis was performed after eliminating these two factors. In the normal weight group, the effect of ARV\textsubscript{SBP} on CVEs in all subgroups (except Q2) remained unchanged, with the risk slightly lower than that in the previous Cox model. This may have occurred because the lower SBP and BPV in the population with normal BP weakened the prediction of ARV\textsubscript{SBP} on CVEs. This finding may have also been due to the fact that participants with hypertension or undergoing antihypertensive therapy were data-processed and might have had lesions of the related target organ, increasing the risk of CVEs.

This study has two major strengths. First, a competitive risk model was adopted for the second risk assessment to more accurately estimate the risk of CVEs. Second, this study is important for clinical and public health. It may allow clinicians to recommend that people who are overweight or obese lose weight and prevent CVEs by controlling BP and BPV. For people of normal weight with hypertension, clinicians may advise against obesity and should pay more attention to the BPV while controlling BP.

This study also has some limitations. First, the research population was limited to Kailuan Group employees, most of whom lived in communities in North China. Thus, the findings of this study may not be applicable to other populations. Nevertheless, the homogeneity of our cohort reduced the potential confounders, and the large sample size of the study is highly instructive for the Chinese population. Second, measurements of BP were only obtained from physical examination data; no information on home BP or multiple BP measurements in 1 year was collected. However, the BP measurements in this study spanned 8 years, with a total of four measurement times, and BP was still a significant predictor of CVEs. Third, the large proportion of men in this study may have affected the prediction of CVEs. However, the average age of the study population was 47.6 years; thus, the effect of sex on the incidence of CVEs was weak.

CONCLUSION
BMI and ARV\textsubscript{SBP} are risk factors for CVEs. As BMI and ARV\textsubscript{SBP} increase, the risk of CVEs increases accordingly. However, the effect of visit-to-visit BPV on the risk of CVEs mainly varies in different BMI groups, especially in the normal weight group.

Author affiliations
\textsuperscript{1}Cardiology, First Hospital of Medical College of Shantou University, Shantou, Guangdong, China
\textsuperscript{2}Cardiology, Shantou University Medical College, Shantou, Guangdong, China
\textsuperscript{3}Cardiology, Second Affiliated Hospital of Shantou University Medical College, Shantou, Guangdong, China
\textsuperscript{4}Foreign Language, Guangdong Polytechnic Normal University, Guangzhou, Guangdong, China
\textsuperscript{5}Department of Cardiology, Kailuan General Hospital, Tangshan, Hebei, China

Twitter Jianhuan Huang @No

Acknowledgements We sincerely express our gratitude to all parties in the Kailuan Study, as well as members of Kailuan General Hospital and its affiliated hospitals.

Contributors HC, SW and YC take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. HC and JH carried out the statistical analysis. ZKC, WW and ZCC participated in the study design. XY and SW strictly reviewed the manuscript. All of the authors read and approved the final draft of the manuscript.

Funding This work was supported by the National Natural Science Foundation of China (No. 81870312).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was in accordance with the Helsinki Declaration and approved by the Ethics Committee of Kailuan General Hospital, and the written informed consents signed by all individuals in the observation group.
Open access

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Datasets that were generated and analysed in this study will not be published because of data protection, but the appropriate authors may have access to and/or analyse the datasets of the current study if reasonably required.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Haojia Chen http://orcid.org/0000-0001-7310-2778
Younen Chen http://orcid.org/0000-0002-4960-3725

REFERENCES
1 Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the global burden of disease study 2013. Lancet 2014;384:766–81.
2 Friedrich MJ. Assessing and addressing global malnutrition. J Am Med Assoc 2015;313.
3 Li Z, Snieder H, Su S, et al. A longitudinal study of blood pressure variability in African-American and European American youths. J Hypertens 2010;28:715–22.
4 Chen H, Zhang R, Zheng Q, et al. Impact of body mass index on long-term blood pressure variability: a cross-sectional study in a cohort of Chinese adults. BMC Public Health 2018;18:1193.
5 Brunner EJ, Shipley MJ, Ahmad-Abbati S, et al. Adiposity, obesity, and arterial aging: longitudinal study of aortic stiffness in the Whitehall II cohort. Hypertension 2015;66:294–300.
6 Murray CJL, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the global burden of disease study 2010. Lancet 2012;380:2197–223.
7 Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects), Lu Y, Haffajeethali K, et al. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1·8 million participants. Lancet 2014;383:970–83.
8 Stevens SL, Wood S, Koshtiari C, et al. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. BMJ 2016;354:i4098.
9 Wilson PWF, D’Agostino RB, Sullivan L, et al. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. Arch Intern Med 2002;162:1867–72.
10 Wu S, Huang Z, Yang X, et al. Prevalence of ideal cardiovascular health and its relationship with the 4-year cardiovascular events in a northern Chinese industrial city. Circ Cardiovasc Qual Outcomes 2012;5:487–93.
11 Jin C, Chen S, Vaidya A, et al. Longitudinal change in fasting blood glucose and myocardial infarction risk in a population without diabetes. Diabetes Care 2017;40:1565–72.
12 Sega R, Cesana G, Bombelli M, et al. Seasonal variations in home and ambulatory blood pressure in the PAMELA population.

Pressione Arteriose Monitorate E Loro Associazioni. J Hypertens 1998;16:1585–92.

13 Wu C, Shlipak MG, Stawski RS, et al. Visit-to-Visit blood pressure variability and mortality and cardiovascular outcomes among older adults: the health, aging, and body composition study. Am J Hypertens 2017;30:151–8.
14 Gao S, Hendrie HC, Wang C, et al. Redefined blood pressure variability measure and its association with mortality in elderly primary care patients. Hypertension 2014;64:45–52.

15 Dadouche-Djelil AM, de la Peña E, Di BI, et al. Brain blood pressure variability and the risk of all-cause mortality, incident myocardial infarction, and incident stroke in the cardiovascular health study. Am J Hypertens 2013;26:1210–7.

16 Shimbo D, Newman JD, Aragaki AK, et al. Association between annual visit-visit blood pressure variability and stroke in postmenopausal women: data from the women’s health initiative. Hypertension 2012;60:625–30.

17 Zakopoulos NA, Tsivgoulis G, Barlas G, et al. Time rate of blood pressure variation is associated with increased common carotid artery intima-media thickness. Hypertension 2005;45:506–12.

18 Mena L, Pintos S, Queipo NV, et al. A reliable index for the prognostic significance of blood pressure variability. J Hypertens 2005;23:505–11.

19 Haidl CE, Jonson P, Coleman H, et al. Long-Term and ultra long-term blood pressure variability during follow-up and mortality in 14,522 patients with hypertension. Hypertension 2013;62:698–705.

20 Mena LJ, Felix VG, Melgarejo JD, et al. 24-Hour blood pressure variability assessed by average real variability: a systematic review and meta-analysis. J Am Heart Assoc 2017;6:e006895.

21 Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypotension. Lancet 2010;375:895–905.

22 Filomena J, Riba-Llena I, Vinyoles E, et al. Short-Term blood pressure variability and blood pressure variability assessed by average real variability: a systematic review and meta-analysis. J Am Heart Assoc 2013;2:75:79–92.

23 Mahmud A, Feely J. Favourable effects on arterial wave reflection and pulse pressure amplification of adding angiotensin II receptor blockers to risk factors of related diseases in Chinese adult population. J Hypertens 2005;23:505–11.

24 Manisty CH, Hughes AD. Meta-Analysis of the comparative effects of different classes of antihypertensive agents on brachial and central systolic blood pressure, and augmentation index. Br J Clin Pharmacol 2013;75:79–92.

25 Zhao B. Coorperative meta-analysis group of China obesity Task force. Predictive values of body mass index and waist circumference to risk factors of related diseases in Chinese adult population 2002:23:5–10.

26 Rothwell PM, Howard SC, Dolan E, et al. Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. Lancet Neurology 2010;9:469–80.

27 Webb AJS, Fischer U, Mehta Z, et al. Effects of antihypertensive drug class on interindividual variation in blood pressure and risk of stroke. Lancet Neurol 2010;9:469–80.

28 Daiong S, Song L, Li X, et al. Association of visit-to-visit blood pressure variability with the risk of all-cause mortality and cardiovascular events in general population. J Clin Hypertens 2018;20:280–8.

29 Tian J, Venn A, Otahal P, et al. The association between quitting smoking and weight gain: a systematic review and meta-analysis of prospective cohort studies. Obes Rev 2015;16:883–901.

30 Ragueneau E, Michaud P, Demolis JL, et al. Effects of cigarette smoking on short-term variability of blood pressure in smoking and non smoking healthy volunteers. Fundam Clin Pharmacol 1999;13:501–7.