Association between blood pressure categories and cardiovascular disease mortality in China

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Abstract

Background

Blood pressure (BP) categories are useful to simplify prevention in public health, and diagnostic and treatment approaches in clinical practice. Updated evidence about the associations of BP categories with cardiovascular diseases (CVDs) and its subtypes is warranted.

Methods and findings

About 0.5 million adults aged 30 to 79 years were recruited from 10 areas in China during 2004–2008. The present study included 430 977 participants without antihypertension treatment, cancer, or CVD at baseline. BP was measured at least twice in a single visit at baseline and CVD deaths during follow-up were collected via registries and the national health insurance databases. Multivariable Cox regression was used to estimate the associations between BP categories and CVD mortality.

Overall, 16.3% had prehypertension-low, 25.1% had prehypertension-high, 14.1% had isolated systolic hypertension (ISH), 1.9% had isolated diastolic hypertension (IDH), and 9.1% had systolic-diastolic hypertension (SDH). During a median 10-year follow-up, 9660 CVD deaths were documented. Compared with normal, the hazard ratios (95% CI) of prehypertension-low, prehypertension-high, ISH, IDH, SDH for CVD were 1.10 (1.01–1.19), 1.32 (1.23–1.42), 2.04 (1.91–2.19), 2.20 (1.85–2.61), and 3.81 (3.54–4.09), respectively. All hypertension subtypes were related to the increased risk of CVD subtypes, with a stronger association for hemorrhagic stroke than for ischemic heart disease. The associations were stronger in younger than older adults.
Conclusions
Prehypertension-high should be considered in CVD primary prevention given its high prevalence and increased CVD risk. All hypertension subtypes were independently associated with CVD and its subtypes mortality, though the strength of associations varied substantially.

Introduction
Hypertension is the most important risk factor for cardiovascular disease (CVD) [1]. According to single or combined elevations of systolic blood pressure (SBP) and diastolic blood pressure (DBP), hypertension is frequently classified into isolated systolic hypertension (ISH), isolated diastolic hypertension (IDH), and systolic-diastolic hypertension (SDH). The associations with CVD might vary among hypertension subtypes because of their different pathophysiological mechanisms [2,3]. Previous studies had demonstrated definite evidence for the CVD risk of ISH and SDH but the effect of IDH was inconclusive [4–6]. Moreover, a continuous and positive association with CVD had been demonstrated above SBP 115–120 mm Hg [7,8]. There is a growing concern about the CVD risk of SBP 120 mm Hg to 140 mm Hg. The Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) introduced a category as prehypertension with BP level of 120 to 139/80 to 89 mm Hg [9]. However, evidence about the CVD risk of prehypertension remains controversial [10,11]. A meta-analysis demonstrated that the increased CVD mortality was largely driven by the high-range of prehypertension [12]. In the 2017 American College of Cardiology/American Heart Association (ACC/AHA) BP guideline, SBP 130–139 and/or DBP 80–89 mm Hg was newly defined as “Hypertension stage 1” [13]. Current evidence found that “Hypertension stage 1” was associated with the increased CVD risk among the younger adults but studies conducted among the older did not find an increased risk, partly due to their small sample size of older adults [14–16]. According to the 2017 ACC/AHA guideline, both the prevalence of hypertension and the number of participants who should take antihypertension treatments increase dramatically [17]. Moreover, during the COVID-19 pandemic, individuals with CVD were more vulnerable to COVID-19 and had a greater risk of developing into a severe condition [18]. Therefore, to clarify the role of “Hypertension stage 1” on the development of CVD, especially among the older adults, is warranted for making prevention strategies about this BP group.

Besides, cerebrovascular diseases have been the top leading cause of mortality in China [19]. Moreover, hemorrhagic stroke accounted for a larger proportion in the Chinese population than western populations [20] and the mortality from hemorrhagic stroke was higher than that from ischemic stroke [21]. However, there is limited evidence for the associations of BP categories with the major subtypes of cardiovascular disease (i.e., ischemic heart disease, ischemic stroke, and hemorrhagic stroke) in a Chinese population. We hypothesized that the newly defined hypertension was associated with increased CVD risk across a wide range of age, and the strength of the association of different hypertension subtypes with CVD and its subtypes might vary. We aimed to provide more detailed information about the associations of BP categories with overall and specific CVD mortality based on the China Kadoorie Biobank (CKB) study.
Materials and methods

Study population

Details of the CKB study design and methods have been reported elsewhere [22,23]. The CKB is a community-based prospective cohort study, involving over 0.5 million adults from 10 areas of China between 2004 and 2008. All men and women aged 30–79 years who were permanently resident and without major disability in each administrative unit were identified and invited to participate [22]. Ethics approvals were obtained from the Ethical Review Committee of Oxford University, the China National Center for Disease Control and Prevention (CDC), and from institutional research boards at the local CDCs in the 10 regions, and all participants provided written informed consent. The study was in accordance with the Declaration of Helsinki.

For the current study, we excluded participants with missing data for covariates (n = 49), or with implausible censoring date (n = 1), or with CVD or cancer at baseline (n = 25 511). Moreover, we further excluded participants with the antihypertension treatment at baseline (n = 65 168), because both dose and types of antihypertensive medications may influence BP levels and lead to misclassification of BP categories. Finally, we included 430 977 participants in the main analyses. By December 31, 2016, 4434 (1.03%) participants were lost to follow-up.

Assessment of BP categories

BP was measured twice by trained staff using a UA-779 digital monitor after they remained at rest in the seated position for at least 5 minutes [24]. If the difference between the two measurements was >10 mm Hg for SBP, a third measurement was required. Only the last two readings were recorded and used to calculate the average of SBP and DBP [7].

According to the JNC-7, BP categories were defined into five groups 1) normal (SBP <120 and DBP <80 mm Hg); 2) prehypertension (SBP 120–139 and/or DBP 80–89 mm Hg); 3) ISH (SBP ≥140 and DBP <90 mm Hg); 4) IDH (SBP <140 and DBP ≥90 mm Hg); 5) SDH (SBP ≥140 and DBP ≥90 mm Hg) [9]. In the 2017 ACC/AHA hypertension guideline, hypertension was defined as SBP ≥130 mmHg and/or DBP ≥90 mmHg [13]. To estimate the effect of “Elevated” and “Hypertension stage 1” in the 2017 ACC/AHA hypertension guideline, we further divided prehypertension into prehypertension-low (equal to “Elevated”, SBP 120–129 and DBP <80 mm Hg) and prehypertension-high (equal to “Hypertension stage 1”, SBP 130–139 and/or DBP 80–89 mm Hg) [13].

Assessment of covariates

Potential confounding variables in this study included sociodemographic characteristics (age, sex, education, and marital status), lifestyle behaviors (tobacco smoking, alcohol consumption, physical activity, and consumption of red meat, fresh fruits, and vegetables), diabetes, menopausal status for female only, and family medical history (heart attack, stroke). Physical activity was calculated by multiplying the metabolic equivalent tasks (METs) value for a particular type of physical activity by hours spent on that activity per day and summing the MET-hours for all activities for each day.

Height, body weight, and heart rate were measured by trained staff. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Prevalent diabetes was defined as a measured fasting blood glucose concentration of ≥7.0 mmol/L, a measured random blood glucose concentration of ≥11.1 mmol/L, or self-reported diagnoses of diabetes.
Assessment of outcomes

The vital status of participants was collected through linkage with regional disease and death registries, and with the new national health insurance databases. To minimize the underreporting of deaths, we also carried out active follow-up annually, by reviewing residential records, visiting local communities, or directly contacting participants [23].

All deaths were coded using the 10th International Classification of Diseases (ICD-10). The main outcome measures in our analysis were mortality from CVD (ICD-10 codes I00 to I99), ischemic heart disease (I20 to I25), myocardial infarction (I21 to I23), cerebrovascular disease (I60 to I69), hemorrhagic stroke (I61), and ischemic stroke (I63).

Statistical analysis

Baseline characteristics were described as means and standard errors or percentages in each BP category, with adjustment for age, sex, and survey sites as appropriate, using either multiple linear regression (for continuous variables) or logistic regression (for categorical variables).

Person-years at risk were calculated from the baseline to the date of death, loss to follow-up, or 31 December 2016, whichever occurred first. Cox proportional hazard models, stratified by age at risk (in 5-year intervals), sex, and survey sites (10 regions), were used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) for CVD mortality related to BP categories, with age as the timescale. The proportional hazards assumption was checked using the Schoenfield residuals, and no violation was observed. The associations of BP categories with mortality from total CVD and its subtypes were assessed after adjustment for age (continuous) at recruitment; and subsequently adjusted for the level of education (no formal or primary school, middle school or high school, or college or higher), marital status (married, or others), smoking status (5 categories: never or occasional smoker, ex-smoker who quit not because of illness, ex-smoker who quit because of illness and current smoker divided into 3 groups according to cigarette equivalents/day [≤15, 15−25, >25]), alcohol consumption (7 categories: never or occasional or seasonal drinker, ex-regular drinker of reduced intake, 1 to 5 days/week, almost daily drinker divided into 4 groups according to total grams of alcohol [≤15, 15−<30, 30−<60, ≥60]), intake frequencies of red meat, fresh fruits, and vegetables (daily, 4−6 days/week, 1−3 days/week, or monthly, rarely or never), physical activity in MET-hours a day (continuous), survey seasons (spring: summer: June, July, August; autumn: winter: December, January, February), menopausal status (for female only, postmenopausal or others); and finally further adjustment for prevalent diabetes at baseline, family medical history, BMI (continuous), and heart rate (continuous). The Nelson-Aalen method was used to describe the cumulative hazard of CVDs during the follow-up across BP categories.

Moreover, we conducted subgroup analyses by age (30−49, 50−59, or 60−79 years), sex (male or female), and survey sites (10 areas) and the interaction effect was estimated by adding a cross-product term (e.g., age groups × BP categories) to the Cox model. In sensitivity analyses, we 1) investigated the associations between BP categories and CVD mortality after excluding the first 2 years of follow-up; or excluding those who had diabetes at baseline; 2) compared the risk of ISH, IDH, and SDH with further controlling SBP or DBP by conducting analyses in the range of SBP/DBP level of 140−159/90−99 mm Hg and of ≥160/100 mm Hg separately.

Statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). All P values were two-sided, and we defined statistical significance as P <0.05.

Results

Baseline characteristics of participants by BP categories

Among 430 977 participants, the mean age was 50.6 years, 58.7% were female, and 57.6% were from rural areas. Overall, 16.3% had prehypertension-low, 25.1% had prehypertension-high,
14.1% had ISH, 1.9% had IDH, and 9.1% had SDH. The prevalence of ISH in older participants was higher than that in younger, while the opposite was observed for IDH (Fig 1).

Compared with normal BP, participants with prehypertension-low, prehypertension-high, or hypertension subtypes were older (except for IDH \( P = 0.10 \)) and were less likely to be female, had a lower level of education (except for IDH \( P = 0.99 \)), were more likely to live in rural areas (except for IDH \( P = 0.32 \)), were less likely to smoke but more likely to drink regularly, were more likely to consume red meat (except for prehypertension-low \( P = 0.33 \)) but less likely to consume fresh fruit, had a higher level of BMI and heart rate, and had a higher prevalence of diabetes (Table 1). The distribution of baseline characteristics of the study population without adjustment for age, sex, and survey sites was presented in S1 Table.

**Association of BP categories with CVD mortality**

During 4.3 million person-years of follow-up (mean duration of follow-up: 10.0 years; median 10.2 years), there were 9660 deaths from CVD, 3564 from ischemic heart diseases (including 2248 myocardial infarction), and 5168 from cerebrovascular diseases (including 3092 hemorrhagic strokes and 965 ischemic strokes).

With normal BP as the reference, prehypertension had a higher risk of overall CVD, cerebrovascular disease, and hemorrhagic stroke (S2 Table). Similar patterns were also observed for prehypertension-low and prehypertension-high (Table 2). Besides, prehypertension-high was related to the increased risk of ischemic heart disease and ischemic stroke. All hypertension subtypes were associated with the increased mortality of overall CVD and its subtypes, after basic- or multi-adjustment for potential confounding factors (S3 Table). The multi-adjusted HRs for overall CVD were highest for SDH (adjusted HR, 3.81 [95%CI, 3.54 to 4.09]), followed by IDH (2.20 [95%CI, 1.85 to 2.61]), ISH (2.04 [95%CI, 1.91 to 2.19]), prehypertension-high (1.32 [95%CI, 1.23 to 1.42]), and finally prehypertension-low (1.10 [95%CI, 1.01 to 1.19]) (Table 2). The Nelson-Aalen curves of the cumulative hazard of CVDs visually showed that SDH had the highest hazard curve (S1 Fig).

**Fig 1. Percentages of blood pressure categories across different age groups.**

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Subgroup and sensitivity analyses

Prehypertension-high and all hypertension subtypes were associated with increased CVD mortality among all age groups (Fig 2). Moreover, we observed stronger associations in younger participants than older ones (all $P$ values for interaction $<0.005$, except for ischemic stroke $P = 0.20$). Heterogeneity by sex was observed for overall CVD, ischemic heart disease, cerebrovascular diseases, and hemorrhagic stroke (S4 Table). S5 Table shows the associations between BP categories and CVD mortality across 10 survey sites. There was a statistically significant interaction between BP categories and survey sites ($P$ for interaction $= 0.016$).

The associations between BP categories and CVD mortality were not materially altered after excluding the first 2 years of follow-up (S6 Table) or excluding participants who had diabetes at baseline (S7 Table). In hypertension, the multivariable-adjusted HR of SDH for CVD

### Table 1. Baseline characteristics of the study population by baseline BP categories.

| Characteristic                  | Normal          | Prehypertension-low | Prehypertension-high | ISH   | IDH   | SDH   |
|---------------------------------|-----------------|---------------------|----------------------|-------|-------|-------|
| Total, No.                      | 144 765         | 70 130              | 107 960              | 60 708| 8387  | 39 027|
| Age, mean (SE), y               | 47.7 (0.03)     | 50.5 (0.04)         | 50.5 (0.03)          | 58.0 (0.04)| 47.9 (0.11)| 53.0 (0.05)|
| Female, No. (%)                 | 96 918 (66.1)   | 39 937 (56.9)       | 58 329 (54.0)        | 35 134(60.2) | 3794 (44.7) | 18 784 (49.0) |
| Education level, No. (%)        |                 |                     |                      |       |       |       |
| No formal education or primary  | 59 294 (48.5)   | 35 191 (49.8)       | 53 136 (49.2)        | 40 644| 3246  | 21 588|
| Middle or high school           | 73 853 (45.0)   | 31 459 (44.7)       | 49 166 (45.4)        | 18 249| 4442  | 12 576|
| College or higher               | 11 618 (6.5)    | 3480 (5.5)          | 5658 (5.5)           | 1815  | 699   | 2218  |
| Rural area, No. (%)             | 73 840 (50.1)   | 42 291 (60.2)       | 65 486 (60.6)        | 37 856| 4324  | 11 388|
| Married, No. (%)                | 134 038 (91.3)  | 64 446 (91.8)       | 99 571 (91.7)        | 52 636| 7849  | 35 419|
| Regular smoking, No. (%)        | 33 951 (29.0)   | 20 331 (27.7)       | 32 518 (27.0)        | 16 082| 14 868| 15 062|
| Male                            | 31 785 (66.5)   | 19 323 (63.6)       | 31 197 (62.4)        | 15 147| 14 740| 15 080|
| Female                          | 2166 (3.1)      | 1008 (2.4)          | 1321 (2.2)           | 935   | 65    | 240   |
| Regular alcohol intake, No. (%) | 15 732 (13.5)   | 10 150 (14.1)       | 19 655 (16.0)        | 9628  | 2196  | 9724  |
| Male                            | 13 635 (29.5)   | 9330 (20.4)         | 18 320 (35.6)        | 8875  | 2085  | 9239  |
| Female                          | 2097 (2.3)      | 820 (2.0)           | 1335 (2.2)           | 753   | 111   | 485   |
| Average weekly consumption, mean (SE), day/week | | | | | | |
| Fresh vegetables                | 6.82 (0.002)    | 6.82 (0.002)        | 6.82 (0.002)         | 6.82  | 6.81  | 6.81  |
| Fresh fruits                    | 2.59 (0.006)    | 2.48 (0.008)        | 2.48 (0.007)         | 2.37  | 2.44  | 2.30  |
| Red meat                        | 3.90 (0.006)    | 3.91 (0.008)        | 3.96 (0.006)         | 3.96  | 3.99  | 3.94  |
| Postmenopausal, No. (%)         | 33 002 (49.7)   | 18 865 (48.5)       | 27 871 (49.1)        | 26 430| 1447  | 11 023|
| Physical activity, mean (SE), MET- hr/day | 21.9 (0.03) | 22.3 (0.05) | 21.9 (0.04) | 21.8 (0.05) | 21.1 (0.13) | 21.6 (0.06) |
| Heart rate, mean (SE), bpm       | 76.2 (0.03)     | 77.7 (0.04)         | 79.7 (0.03)          | 79.8  | 82.9  | 83.1  |
| Body mass index, mean (SE), kg/m²| 22.4 (0.01)    | 23.3 (0.01)         | 23.8 (0.01)          | 24.3  | 24.0  | 24.9  |
| Diabetes, No. (%)               | 3574 (2.6)      | 2635 (3.9)          | 4847 (4.7)           | 5177  | 366   | 2409  |
| Family medical history, No. (%) | 25 525 (17.2)   | 12 555 (18.2)       | 21 193 (19.7)        | 11 662| 2012  | 9347  |
| Heart attack                    | 4707 (3.0)      | 2078 (3.1)          | 3314 (3.1)           | 1613  | 338   | 1329  |
| Stroke                          | 21 875 (14.9)   | 10 918 (15.8)       | 18 684 (17.3)        | 10 445| 1772  | 8390  |
| SBP, mean (SE), mmHg            | 109.7 (0.02)    | 124.3 (0.03)        | 129.8 (0.03)         | 150.0 | 133.5 | 161.8 |
| DBP, mean (SE), mmHg            | 68.0 (0.02)     | 72.4 (0.02)         | 80.1 (0.02)          | 81.4  | 92.1  | 97.6  |

Abbreviations: BP, blood pressure; SE, standard error; MET, metabolic equivalent of task; bpm, beat per minute.

* All variables were adjusted for age, sex, and survey sites when appropriate.

* Average weekly consumptions of red meat, fresh vegetables, and fruits were calculated by assigning participants to the midpoint of their consumption category.

* Only for female.

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mortality was higher than that of ISH and IDH ($P < 0.001$), while the effect of ISH on CVD mortality was almost similar to that of IDH (S2 Fig).

### Discussion

The present study, involving more than 0.4M people living in China, found that both prehypertension-low and prehypertension-high were associated with higher CVD mortality independent of other cardiovascular risk factors. All hypertension subtypes were associated with increased mortality from overall CVD and CVD subtypes, and the CVD risk of SDH was
higher than that of ISH and IDH. The associations between BP categories and cerebrovascular diseases were stronger than for ischemic heart diseases. Furthermore, the associations between BP categories and CVD mortality were stronger in younger participants than in older ones.

The 2017 ACC/AHA hypertension guideline defined the 130-139/80-89 mm Hg as “Hypertension stage 1” [13]. Based on the guideline, about a quarter of participants (i.e., prehypertension-high) in our study would be newly defined as hypertension. Previous studies found an increased CVD risk of this BP category in younger adults, which was consistent with our results [15,25]. However, the findings were mixed in older adults. Some studies reported that this BP category was not associated with the increased CVD risk [15,25], while others reported a slightly higher CVD mortality for those aged ≥65 years (HR [95%CI]: 1.22 [1.04 to 1.44]) [26]. In our study, the CVD risk of this BP category became weaker in participants aged 60 to 69 years.

Fig 2. Associations of BP categories with mortality from CVDs and its major subtypes by age groups. Abbreviations: BP, blood pressure; CVDs, cardiovascular diseases; HR, hazard ratios; CI, confidence interval. Reference was normal BP. Multi-adjusted HR were adjusted for age, education level, marital status, smoking status, alcohol consumption, intake frequencies of vegetables, fruits, and red meat, physical activity, body mass index, survey season, heart rate, diabetes at baseline, family history of heart attack, stroke (only adjusted for in corresponding analysis of cause-specific mortality) and were stratified according to sex and survey sites. Statistically significant heterogeneity was observed in the associations between blood pressure categories and CVD mortality across age groups (all P values for interaction <0.005, except for ischemic stroke P = 0.20). Data markers represent the point estimate of hazard ratio. Error bars represent 95% confidence interval. Black arrows represent the confidence intervals exceed the X-axis value.

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79 years, but there was still a 22% higher CVD mortality than the normal BP. Moreover, this BP category was associated with increased mortality from CVD subtypes, especially for hemorrhagic stroke, with a 69% higher risk compared to normal BP. Given the high prevalence of cerebrovascular diseases, especially hemorrhagic stroke in China [20], managing the BP of that newly defined hypertension in the public health practice may benefit for reducing the CVD burden.

Previous studies have reported consistent associations of both ISH and SDH with the CVD mortality [4,6,27], and clinical trial also detected that individuals with ISH or SDH could benefit from antihypertensive treatment [28], but whether IDH was associated with an increased CVD risk was still controversial [4,5,29]. In the current study, all hypertension subtypes were related to the increased mortality from CVD and specific CVDs, and IDH was at least as important as ISH in predicting future CVD mortality. These results also supported current guidelines which recommended pharmacologic treatments based on DBP as well as SBP [9,30]. In line with previous studies [4,6], the present study demonstrated that SDH conferred the highest CVD risk, followed by IDH and ISH. The heterogeneity among hypertension subtypes might be explained by the higher mean level of SBP or DBP of SDH than that of ISH or IDH. However, after controlling for SBP or DBP, the CVD risk of SDH was still higher than that of ISH. Similar results were also observed for cerebrovascular disease, hemorrhagic stroke, and ischemic stroke. Our finding suggested that incorporating SBP and DBP might improve the prediction of CVD risk models, and future studies are needed to clarify potential mechanisms for the heterogeneity among hypertension subtypes. Likewise, we also identified that the strength of the associations between hypertension subtypes and specific CVD mortality varied significantly, with stronger for cerebrovascular disease than for ischemic heart disease, and extreme for hemorrhagic stroke than for ischemic stroke.

Previous literature found that the associations between BP categories and CVD deaths varied by age, with a stronger association in younger adults than older ones [6,31]. Consistent with these findings, we also identified stronger associations between BP categories and major CVDs (except ischemic stroke) among younger compared with older. Additionally, the mechanisms of ISH in young are still unclear. Some studies showed that in young and middle-aged adults, ISH was “pseudo” or “spurious” hypertension attributed to amplification of central aortic waveform, while others found ISH might be related to increased stroke volume and aortic stiffness [32–34]. However, the increased CVD risk of ISH in the current study indicated the terms “pseudo” or “spurious” hypertension might be unjustified.

To the best of our knowledge, this is the largest prospective study to investigate the associations of BP categories with mortality from CVD and its major subtypes in a Chinese population. The chief strengths of this study included the unified standard methods for collecting information, the sufficient number of CVD outcomes, and the rigorous check of diagnosis of CVD. This study also had several limitations. First, BP was obtained in a single baseline survey, without considering the fluctuation of BP in the daytime, which may misclassify individuals with “white-coat hypertension” or “masked hypertension” [35,36]. However, it is not feasible to monitor ambulatory BP for each participant in a large-scale population study. Second, we excluded participants who taking antihypertensive medicines, which might cause selection bias and limit the extrapolation of our findings. However, antihypertensive medication would affect the patients’ blood pressure level, leading to misclassification of BP categories. Hence, it is more reasonable to restrict study participants without antihypertensive treatment. Third, elevated low-density lipoprotein (or total) cholesterol, a risk factor for CVD [37], was not available in the present study. A meta-analysis reported that total cholesterol (TC) was positively associated with ischemic heart disease mortality, but there was rather a weak association of TC with mortality from cerebrovascular disease and hemorrhagic stroke [38]. Therefore,
failing to adjust for TC is unlikely to have any appreciable impact on the associations with cerebrovascular disease in our study. Fourth, under-reporting of cardiovascular deaths might have occurred during follow-up, but the probability of under-reported would not depend on BP categories, and we also used multiple ways to minimize the under-reporting of deaths.

**Conclusion**

The definition of hypertension is one of the most notable changes in the 2017 ACC/AHA hypertension guideline. The present study provided important evidence about the long-term CVD risk of those new hypertensives (i.e., “Hypertension stage 1” in 2017 guideline and prehypertension-high in the current study) and highlighted its important role in CVD primary prevention, both due to the high prevalence and be associated with higher CVD mortality. All hypertension subtypes were related to the increased mortality from CVDs, especially from hemorrhagic strokes, and should be considered in BP management regardless of age and gender.

**Supporting information**

S1 Checklist. STROBE statement for observational studies.

(S1 Fig) Nelson-Aalen cumulative hazard for cardiovascular diseases according to the blood pressure categories.

(S2 Fig) Associations of ISH, IDH, and SDH with mortality from CVDs and its major subtypes in stage 1 hypertension, stage 2 hypertension and total hypertension.

(S1 Table) Baseline characteristics of the study population by baseline BP categories.

(S2 Table) Associations of blood pressure categories with cardiovascular diseases mortality among 430,977 participants.

(S3 Table) Associations of blood pressure categories with mortality from cardiovascular diseases and its major subtypes. Values are hazard ratios (95% confidence interval).

(S4 Table) Associations of prehypertension and hypertension subtypes with mortality from cardiovascular diseases and its major subtypes by sex.

(S5 Table) Associations of prehypertension and hypertension subtypes with mortality from cardiovascular diseases by survey sites.

(S6 Table) Associations of blood pressure categories with deaths due to cardiovascular diseases among participants excluding the first two years of follow-up.

(S7 Table) Associations of blood pressure categories with deaths of cardiovascular diseases among non-diabetes participants at baseline.
S1 Text. Baseline questionnaire in the China Kadoorie Biobank study.

(DOCX)

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References

1. World Health Organization. A global brief on hypertension: silent killer, global public health crisis 2013. Available from http://www.who.int/cardiovascular_diseases/publications/global_brief_hypertension/en/.

2. Verdecchia P, Angeli F. Natural history of hypertension subtypes. Circulation. 2005; 111(9):1094–6. https://doi.org/10.1161/01.CIR.0000158690.78503.5F PMID: 15753224

3. Ma Y, Yabluchanskiy A, Lindsey ML, Chilton RJ. Is isolated systolic hypertension worse than combined systolic/diastolic hypertension? J Clin Hypertens. 2012; 14(11):808–9. https://doi.org/10.1111/jch.12011 PMID: 23126357

4. Arima H, Murakami Y, Lam TH, Kim HC, Ueshima H, Woo J, et al. Effects of prehypertension and hypertension subtype on cardiovascular disease in the Asia-Pacific region. Hypertension. 2012; 59 (6):1118–23. https://doi.org/10.1161/HYPERTENSIONAHA.111.187252 PMID: 22547441

5. Li Y, Wei F-F, Thijs L, Boggia J, Asayama K, Hansen TW, et al. Ambulatory hypertension subtypes and 24-hour systolic and diastolic blood pressure as distinct outcome predictors in 8341 untreated people recruited from 12 populations. Circulation. 2014; 130(6):666–74. https://doi.org/10.1161/CIRCULATIONAHA.113.004876 PMID: 24906822

6. Kelly TN, Gu D, Chen J, Huang J, Chen J, Duan X, et al. Hypertension subtype and risk of cardiovascular disease in Chinese adults. Circulation. 2008; 118(15):1558–66. https://doi.org/10.1161/CIRCULATIONAHA.107.725993 PMID: 18809900

7. Lacey B, Lewington S, Clarke R, Kong XL, Chen Y, Guo Y, et al. Age-specific association between blood pressure and vascular and non-vascular chronic diseases in 0.5 million adults in China: a prospective cohort study. Lancet Glob Heal. 2018; 6(6):e641–8.

8. Lewington S, Clarke R, O’zlubash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002; 360(9349):1903–13. https://doi.org/10.1016/s0140-6736(02)11911-6 PMID: 12493255

9. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension. 2003; 42(6):1206–52.

10. Dorjgochoo T, Shu XO, Zhang X, Li H, Yang G, Gao L, et al. Relation of blood pressure components and categories and all-cause, stroke and coronary heart disease mortality in urban Chinese women: a
population-based prospective study. J Hypertens. 2009; 27(3):468–75. https://doi.org/10.1097/HJH.0b013e3282320eb9 PMID: 19262225

11. He J, Gu D, Chen J, Wu X, Kelly TN, Huang J Feng, et al. Premature deaths attributable to blood pressure in China: a prospective cohort study. Lancet. 2009; 374(9703):1765–72. PMID: 19811816

12. Huang Y, Su L, Cai X, Mai W, Wang S, Hu Y, et al. Association of all-cause and cardiovascular mortality with prehypertension: A meta-analysis. Am Heart J. 2014; 167(2):160–168.e1. PMID: 24439976

13. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018; 71(6):e13–115.

14. Son JS, Choi S, Kim K, Kim SM, Choi D, Lee G, et al. Association of blood pressure classification in Korean young adults according to the 2017 American College of Cardiology/American Heart Association guidelines with subsequent cardiovascular disease events. JAMA. 2018; 320(17):1783–92.

15. Qi Y, Han X, Zhao D, Wang W, Wang M, Sun J, et al. Long-term cardiovascular risk associated with stage 1 hypertension defined by the 2017 ACC/AHA hypertension guideline. J Am Coll Cardiol. 2018; 72(11):1201–10.

16. Yano Y, Reis JP, Colangelo LA, Shimbo D, Viera AJ, Allen NB, et al. Association of blood pressure classification in young adults using the 2017 American College of Cardiology/American Heart Association blood pressure guideline with cardiovascular events later in life. JAMA. 2018; 320(17):1774–82. https://doi.org/10.1001/jama.2018.13551 PMID: 30398601

17. Khera R, Lu Y, Lu J, Saxena A, Nasir K, Jiang L, et al. Impact of 2017 ACC/AHA guidelines on prevalence of hypertension and eligibility for antihypertensive treatment in United States and China: nationally representative cross sectional study. BMJ. 2018;k2357. https://doi.org/10.1136/bmj.k2357 PMID: 29997129

18. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020; 323(11):1061–9. https://doi.org/10.1001/jama.2020.1585 PMID: 32031570

19. Zhou M, Wang H, Zeng X, Yin P, Zhu J, Chen W, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2019; 394(10244):1145–58. https://doi.org/10.1016/S0140-6736(19)30427-1 PMID: 31248666

20. Tsai C-F, Thomas B, Sudlow CLM. Epidemiology of stroke and its subtypes in Chinese vs white populations: A systematic review. Neurology. 2013; 81(3):264–72. https://doi.org/10.1212/WNL.0b013e31829bde3 PMID: 23958408

21. Zhou M, Wang H, Zhu J, Chen W, Wang L, Liu S, et al. Cause-specific mortality for 240 causes in China during 1990–2013: a systematic subnational analysis for the Global Burden of Disease Study 2013. Lancet. 2016; 387(10015):251–72. https://doi.org/10.1016/S0140-6736(15)00551-6 PMID: 26510778

22. Chen Z, Lee L, Chen J, Collins R, Wu F, Guo Y, et al. Cohort Profile: The Kadoorie Study of Chronic Disease in China (KSCDC). Int J Epidemiol. 2005; 34(6):1243–9. https://doi.org/10.1093/ije/dyi174 PMID: 16131516

23. Chen Z, Chen J, Collins R, Guo Y, Petö R, Wu F, et al. China Kadoorie Biobank of 0.5 million people: survey methods, baseline characteristics and long-term follow-up. Int J Epidemiol. 2011; 40(6):1652–66. https://doi.org/10.1093/ije/dyr120 PMID: 22158673

24. Longo D, Bertolo O, Toffanin G, Frezza P, Palatini P. Validation of the A&D UA-631 (UA-779 Life Source) device for self-measurement of blood pressure and relationship between its performance and large artery compliance. Blood Press Monit. 2002; 7(4):243–8. https://doi.org/10.1097/00126097-200208000-00007 PMID: 12198341

25. Talaei M, Hosseini N, Koh AS, Yuan J, Koh W. Association of “Elevated Blood Pressure” and “Stage 1 Hypertension” with cardiovascular mortality among an Asian population. J Am Heart Assoc. 2018; 7(8):e008911. https://doi.org/10.1161/JAHA.118.008911 PMID: 29636346

26. Liu N, Yang JJ, Meng R, Pan X-F, Zhang X, He M, et al. Associations of blood pressure categories defined by 2017 ACC/AHA guidelines with mortality in China: Pooled results from three prospective cohorts. Eur J Prev Cardiol. 2020; 27(4):345–54. https://doi.org/10.1177/2047487319862066 PMID: 31288541

27. Yano Y, Stamler J, Garside DB, Davidius ML, Franklin SS, Carnethon MR, et al. Isolated systolic hypertension in young and middle-aged adults and 31-year risk for cardiovascular mortality. J Am Coll Cardiol. 2015; 65(4):327–35. https://doi.org/10.1016/j.jacc.2014.10.066 PMID: 25634830

28. Arima H, Anderson C, Omae T, Woodward M, Hata J, Murakami Y, et al. Effects of blood pressure lowering on major vascular events among patients with isolated diastolic hypertension. Stroke. 2011; 42(8):2339–41. https://doi.org/10.1161/STROKEAHA.110.606764 PMID: 21700945
29. Pickering TG. Isolated diastolic hypertension. J Clin Hypertens. 2003; 5(6):411–3. https://doi.org/10.1111/1524-6175.2003.02840.x PMID: 14688497
30. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 Practice guidelines for the management of arterial hypertension of the European society of cardiology and the European society of hypertension: ESC/ESH task force for the management of arterial hypertension. J Hypertens. 2018; 36(12):2284–309. https://doi.org/10.1097/HJH.0000000000001961 PMID: 30379783
31. Gu D, Chen J, Wu X, Duan X, Jones DW, Huang J, et al. Prehypertension and risk of cardiovascular disease in Chinese adults. J Hypertens. 2009; 27(4):721–9. https://doi.org/10.1097/HJH.0b013e328323ad89 PMID: 19300109
32. McEniery CM, Yasmin, Wallace S, Maki-Petaja K, McDonnell B, Sharman JE, et al. Increased stroke volume and aortic stiffness contribute to isolated systolic hypertension in young adults. Hypertension. 2005; 46(1):221–6. https://doi.org/10.1161/01.HYP.0000165310.84801.e0 PMID: 15867140
33. Yano Y, Neeland IJ, Ayers C, Peshock R, Berry JD, Lloyd-Jones DM, et al. Hemodynamic and mechanical properties of the proximal aorta in young and middle-aged adults with isolated systolic hypertension. Hypertension. 2017; 70(1):158–65. https://doi.org/10.1161/HYPERTENSIONAHA.117.09279 PMID: 28507172
34. Pickering TG. Isolated systolic hypertension in the young. J Clin Hypertens. 2004; 6(1):47–8.
35. Franklin SS, Thijs L, Hansen TW, Li Y, Boggia J, Kikuya M, et al. Significance of white-coat hypertension in older persons with isolated systolic hypertension. Hypertension. 2012; 59(3):564–71. https://doi.org/10.1161/HYPERTENSIONAHA.111.180653 PMID: 2225396
36. de la Sierra A, Vinyoles E, Banegas JR, Parati G, de la Cruz JJ, Gorostidi M, et al. Short-term and long-term reproducibility of hypertension phenotypes obtained by office and ambulatory blood pressure measurements. J Clin Hypertens. 2016; 18(9):927–33. https://doi.org/10.1111/jch.12792 PMID: 26890293
37. Zhu Y, Lu J-M, Yu Z-B, Li D, Wu M-Y, Shen P, et al. Intra-individual variability of total cholesterol is associated with cardiovascular disease mortality: A cohort study. Nutr Metab Cardiovasc Dis. 2019; 29 (11):1205–13. https://doi.org/10.1016/j.numecd.2019.07.007 PMID: 31383502
38. Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55 000 vascular deaths. Lancet. 2007; 370(9602):1829–39. https://doi.org/10.1016/S0140-6736(07)61778-4 PMID: 18061058