Opposing Age-Related Trends in Absolute and Relative Risk of Adverse Health Outcomes Associated with Out-of-Office Blood Pressure

Short Title: Cardiovascular Risk and Out-of-Office Blood Pressure

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Abstract

Participant-level meta-analyses assessed the age-specific relevance of office blood pressure to cardiovascular complications, but this information is lacking for out-of-office blood pressure. At baseline, daytime ambulatory (n=12,624) or home (n=5297) blood pressure were measured in 17,921 participants (51.3% women; mean age, 54.2 years) from 17 population cohorts. Subsequently, mortality and cardiovascular events were recorded. Using multivariable Cox regression, floating absolute risk was computed across four age bands (≤60, 61–70, 71–80 and >80 years). Over 236,491 person-years, 3855 people died and 2942 cardiovascular events occurred. From levels as low as 110/65 mm Hg, risk log-linearly increased with higher out-of-office systolic/diastolic blood pressure. From the youngest to the oldest age group, rates expressed per 1000 person-years increased (P<0.001) from 4.4 (95% confidence interval, 4.0–4.7) to 86.3 (76.1–96.5) for all-cause mortality and from 4.1 (3.9–4.6) to 59.8 (51.0–68.7) for cardiovascular events, whereas hazard ratios per 20-mm Hg increment in systolic out-of-office blood pressure decreased (P≤0.0033) from 1.42 (1.19–1.69) to 1.09 (1.05–1.12) and from 1.70 (1.51–1.92) to 1.12 (1.07–1.17), respectively. These age-related trends were similar for out-of-office diastolic pressure and were generally consistent in both sexes and across ethnicities. In conclusion, adverse outcomes were directly associated with out-of-office blood pressure in adults. At young age, the absolute risk associated with out-of-office blood pressure was low, but relative risk high, whereas with advancing age relative risk decreased and absolute risk increased. These observations highlight the need of a lifecourse approach for the management of hypertension.

Key Words: ambulatory blood pressure monitoring ■ cardiovascular disease ■ home blood pressure ■ hypertension ■ mortality ■ population science

Introduction

High blood pressure (BP) is the major driver of cardiovascular complications.[1-3] Several studies established that out-of-office BP, measured by ambulatory[4,5] or home[6] monitoring is a better predictor of mortality and cardiovascular complications than office BP is. The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guideline for the management of hypertension[7] and other directives[8,9] recommended that for the proper diagnosis and management of hypertension out-of-office BP measurement is a prerequisite. To evaluate the prognostic accuracy of out-of-office BP measurement, our consortium set up the International Databases on Ambulatory (IDACO)[10] and Home (IDHOCO)[11] BP in Relation to Cardiovascular Outcome. This resource is a powerful instrument to assess the relevance of out-of-office BP in a wide array of circumstances, as previously done for office BP as predictor of cardiovascular mortality and morbidity.[1-3] To our knowledge, a similar analysis has never been undertaken for out-of-office BP, including both ambulatory and home BP. Hence, by combining individual participant data from longitudinal population studies, the objective of the present meta-analysis was to characterize the age- sex- and ethnicity-specific relevance of out-of-office BP to the subsequent incidence of mortality and fatal and nonfatal cardiovascular events.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Participants

All cohort studies complied with the Declaration of Helsinki for research in humans,[12] received ethical approval from the competent Institutional Review Boards, and included randomly recruited participants from populations or communities. All participants provided informed written consent. Cohort studies qualified for inclusion, if information on office and out-of-office BP and cardiovascular risk factors was available at baseline, if follow-up included both fatal and nonfatal events, and if study reports had been published in peer-reviewed articles.[10,11] The online-only Supplementary Appendix, available with the full text of this article at http://hyper.ahajournals.org provides further cohort-specific information on the catchment areas, sampling strategies, recruitment, participation rate, and the number of participants enrolled and analyzed, separately for IDACO (Table S1) and IDHOCO (Table S2).

The IDACO database included 13,654 participants from 13 cohort studies,[13-22] who had their ambulatory BP measured (Figure 1). IDHOCO involved 7571 participants from seven studies,[6,17,23-25] who had measured their home BP (Figure 1). We excluded participants from analysis, if they were younger than 18 years (n=314), if their in-office BP had not been measured (n=504), or if they had fewer than 10 daytime ambulatory BP readings (n=176) or fewer than two home BP

measurements (n=18). We also excluded 702 Ohasama participants with incomplete identification, precluding an error-free merging of IDACO and IDHOCO data. In 1590 participants, who underwent both ambulatory and home BP monitoring, we used daytime ambulatory BP as out-of-office BP. Finally, four data sets were available for the statistical analysis (Figure 1): group A consisted of 17,921 participants whose out-of-office BP was based on their daytime ambulatory BP (n=12,624) or on their self-measured home BP (n=5297); group B included 12,624 participants with daytime ambulatory BP; group C included 6887 participants with home BP; and group D 10,864 participants, who in addition to at least 10 daytime BP readings also had 5 or more nighttime ambulatory BP readings, allowing an analysis of the 24-h and nighttime BP (Figure 1).

Blood Pressure Measurement

Portable monitors were programmed to obtain ambulatory BP readings at 30-minute intervals throughout the whole day,[14,21] or at intervals ranging from 15[13] to 30[16] minutes during daytime and from 30[13] to 60[16] minutes at night (Table S3). The same macros written in Statistical Analysis System (SAS) code processed all ambulatory and home BP recordings. While accounting for the daily activities of the participants documented by diaries in 64.1% of IDACO participants[26] and as consistently done in all IDACO articles published since 2007,[4] we defined daytime as the interval from 10:00 h to 20:00 h in Europeans and South Americans, and from 08:00 h to 18:00 h in Asians. The corresponding nighttime intervals ranged from midnight to 06:00 h and from 22:00 h to 04:00 h, respectively. Within individual

subjects, we weighted the means of the ambulatory BP by the time interval between readings. This gives a weight to each individual BP readings in a recording proportional to the preceding time interval.[27] Participants measured their home BP after 5 minutes of rest in the sitting position over periods ranging from a single day[17] up to 30 days[25] (Table S4). All devices used for ambulatory (Table S3) or home (Table S4) BP measurement had passed validation, using established protocols, and were fitted to an upper-arm cuff with an appropriate size for each participant's arm circumference.

Ascertainment of Events

We ascertained vital status and the incidence of fatal and nonfatal diseases from the appropriate sources in each country, as described in previous IDACO[10] and IDHOCO[11] publications. Outcomes were coded according to various versions of the International Classification of Diseases. Events of major interest were total mortality and a composite cardiovascular outcome consisting of cardiovascular mortality combined with nonfatal coronary events, heart failure and stroke. Other events were cardiovascular mortality (ICD8 390–448, ICD9 390.0–459.9, and ICD10 I00–I79 and R96), coronary events (death from ischemic heart disease [ICD8 411–412, ICD9 411 and 414, and ICD10 I20, I24–I25], sudden death [ICD8 427.2 and 795, ICD9 427.5 and 798, and ICD10 I46 and R96], nonfatal myocardial infarction [ICD8/9 410 and ICD10 I21–I22], and coronary revascularization), and stroke (ICD8/9 430–434 and 436, ICD10 I60–I64 and I67–I68), not including transient ischemic attack. Heart failure (ICD8 428, 427.0, 427.1, 427.2, 429, 5191, and 78214, ICD9 429, and ICD10

I50 and J81) was included in the composite cardiovascular endpoint. Its diagnosis required hospitalization in the Scandinavian cohorts.[13,16] In the other cohorts, heart failure was either a clinical diagnosis or the diagnosis on the death certificate. All events were validated against hospital files or medical records held by primary care physicians or specialists. In all outcome analyses, we only considered the first endpoint within each category. No participant was lost to follow-up.

Statistical Analysis

For database management and statistical analysis, we used the SAS system, version 9.4, maintenance level 5 (SAS Institute Inc., Cary, NC). Means were compared using the large-sample z-test and proportions by Fisher's exact test. We computed the 95% confidence intervals (CI) of rates as $R \pm 1.96 \times \sqrt{(R/T)}$, where R and T are the rate and the denominator used to calculate the rate.

Information on serum cholesterol level was not available for the Didima cohort[24] and was, as in previous publications,[28] extrapolated from data stratified by sex and 10-year age bands from the ATTICA population study,[29] which took place at the same time and in the same geographical area as the Didima study. Furthermore, after stratification for cohort and sex, we interpolated missing values of body mass index (n=310) and serum cholesterol (n=942) from the regression slopes on age. In participants with unknown status for smoking (n=205), drinking (n=2024), antihypertensive treatment (n=39), diabetes mellitus (n=4) or history of cardiovascular disease (n=2), we set the design variable to the cohort- and sex-specific mean of the codes (0, 1).

We determined hazard ratios from Cox models stratified by cohort, using the strata option implemented in the PHREG procedure of the SAS software, and adjusted for sex, age, body mass index, serum cholesterol, smoking and drinking, antihypertensive drug treatment and history of diabetes mellitus and cardiovascular disease. While stratifying for cohort, we pooled participants recruited in the framework of the European Project on Genes in Hypertension (Novosibirsk, Kraków, Gdańsk, Pilsen and Padova).[20] Taking into account the incidence of events over the age and BP ranges, we considered four age groups (≤60, 61–70, 71–80 and >80 years) and five BP categories. For daytime, home and 24-h ambulatory BP, the categories were <120, 120–129, 130–139, 140–149 and ≥150 mm Hg systolic and <70, 70–74, 75–79, 80–84 and ≥85 mm Hg diastolic. For the nighttime ambulatory BP, the categories were <110, 110–119, 120–129, 130–139 and ≥140 mm Hg systolic and <60, 60–64, 65–69, 70–74 and ≥75 mm Hg diastolic. For analysis of systolic and diastolic BP, this yielded each time 20 groups, of which the youngest with the lowest BP was taken as reference with a hazard ratio of 1.0. Relative to this, the 19 other hazard ratios associated with BP were estimated simultaneously by Cox regression. This approach allows assigning an error term to each hazard ratio, including that of the reference group and avoids any assumption to be made as to whether the proportional risks associated with BP differ according to age group. Collectively, the 20 hazard ratios are all related to the absolute event rate in the study population by some common constant of proportionality and were presented as floating absolute risks.[30] We checked the proportional hazards assumption and

the functional forms of the covariables by the Kolmogorov-type supremum test. We applied the Lexis expansion[31] for age in Cox regression, which converts one observation per subject (age at entry) into several observations of different age-at-risk bands. This approach allows adjusting for attained age at risk rather than for age at entry. We compared hazard ratios between sexes and ethnic groups, using a normal approximation of the log-transformed point estimates and standard errors. Finally, using Cox regression, we expressed the risks of adverse health outcomes associated with BP for 20 mm Hg and 10 mm Hg increments in systolic and diastolic BP, respectively.

Results

Baseline Characteristics

Of 17,921 participants, 12,624 had their out-of-office BP assessed by daytime ambulatory monitoring and 6887 by self-measurement at home (Table 1). According to ethnicity, 22.2% were Chinese (n=880) or Japanese (n=3091), 62.3% were Eastern Europeans (Czech Republic, Poland and Russian Federation; n=1082), Western Europeans (Belgium, Greece, Ireland and Italy; n=4579) or Scandinavians (Denmark, Finland and Sweden; n=5505), and 15.5% were South Americans mainly of European ancestry (Argentina, Uruguay and Venezuela; n=2784). About half of the study population (51.3%) was female.

In the 17,921 participants with either daytime (n=12,624) or home (n=5297) BP (group A; Figure 1), mean systolic/diastolic values were 129.3/78.2 mm Hg for out-

of-office BP, 129.3/78.8 mm Hg for daytime BP, and 129.1/76.9 mm Hg for home BP. Age at enrolment ranged from 18 to 97 years. Mean values were 54.2 years for age, 25.6 kg/m^2 for body mass index, 5.54 mmol/L for serum cholesterol and 5.28 mmol/L for blood glucose. For smoking the prevalence was 25.6%, 46.6% for drinking, and 50.4% for being overweight or obese; 6.7% of participants had diabetes mellitus and 10.6% a history of cardiovascular disease. The characteristics of the cohorts who had their daytime ambulatory BP (n=12,624; group B) or home BP (n=6887; group C) measured mirrored those of the overall study population (Figure 1 and Table 1). Among 10,864 participants (group D), the 24-h and nighttime BP averaged 123.9/74.0 mm Hg and 112.9/65.1 mm Hg, respectively (Figure 1 and Table 1).

Quality of the Blood Pressure Measurements

Among IDACO participants, the median number of ambulatory readings averaged to estimate the daytime (group B), nighttime (group D) and 24-h blood pressure (group D) was 29 (5th-95th percentile interval, 15–41), 11 (6–13) and 56 (35–82), respectively. Similar data are given for each IDACO cohort separately in Table S3 for the 24-h BP and in Table S5 for the daytime and nighttime BP. In all IDHOCO participants (group C), the median number of home BP readings per individual was 28 (2–56). The corresponding data for each IDHOCO cohort are available in Table S4.

Incidence of Events

The number of person-years of follow-up totaled 236,491 in 17,921 participants, who had either their daytime or home BP measured (group A). Over a median follow-up of 13.2 years (5th-95th percentile interval, 3.5–24.2), 3855 deaths occurred, of which 1441 (37.4%) were cardiovascular. Of 2942 fatal or nonfatal cardiovascular events, 1303 (44.3%) were due to ischemic heart disease and 1174 (39.9%) to stroke. Total and cardiovascular mortality ran at rates of 16.3 (CI, 15.8–16.8) and 6.09 (CI, 5.78–6.41) deaths per 1000 person-years, and cardiovascular events, coronary events and stroke at rates of 13.1 (CI, 12.6–13.5), 5.61 (CI, 5.31–5.92) and 5.08 (CI, 4.79–5.37) events per 1000 person-years with similar estimates in groups B and C (Table S6).

Age-Specific Risk of Death or Cardiovascular Events

Absolute risk of all events increased across the four age strata (Table 2). Figure 2 shows the log-linear associations of total and cardiovascular mortality and fatal and nonfatal cardiovascular events with systolic and diastolic out-of-office BP. The five points plotted for each age group were well fitted by the age-specific regression lines. In all age groups, there was a graded increase in risk with higher category of systolic and diastolic out-of-office BP starting from levels below 110 mm Hg systolic and below 65 mm Hg diastolic. This pattern was consistent for home (group A), daytime (group B), nighttime (group D) and 24-h (group D) systolic (Figure S1) and diastolic (Figure S2) BP. Sensitivity analyses using age at baseline instead of age at risk produced confirmatory results for both systolic and diastolic BP (Figure S3).

Hazard ratios for 20/10 mm Hg increments in systolic/diastolic BP were computed for total mortality and fatal plus nonfatal cardiovascular and coronary events and stroke (Figure 3). For all events under study, relative risk as captured by the multivariable-adjusted hazard ratios increased with age, irrespective of whether age-at-risk (Lexis expansion applied; Figure 3; $P \leq 0.0385$) or age at baseline was used (Lexis expansion not applied; Figure S4; $P \leq 0.0420$). This age-related increase in relative risk was largely persistent, if participants aged ≤60 years were further subdivided into two age bands (51–60 years and ≤50 years, Figure S5), if patients with a history of cardiovascular disease (n=1893 [10.6%]) or those on antihypertensive drug treatment at baseline (n=3721 [20.8%]) were excluded (Figure S6), or if daytime ambulatory and home BPs were analyzed separately (Figure S7). In the 1893 participants with a history of cardiovascular disease, there was no J-curve in the association of total mortality or the composite cardiovascular endpoint with systolic or diastolic out-of-office BP (Figure S8).

Analyses Stratified by Sex and Ethnicity

Across the four age groups, there were no sex differences ($P \geq 0.2004$) in the multivariable-adjusted hazard ratios relating adverse health outcomes to systolic or diastolic out-of-office BP (Figure S9). The study population included 13,950 people of European descent (including South American) and 3971 Asians. Across the four age groups, there were few ethnic differences ($P \geq 0.1148$) in the multivariable-adjusted hazard ratios relating adverse health outcomes to systolic or diastolic out-of-office BP (Figure S10). In the age band from 71 to 80 years (Figure S10), Asians

compared with Europeans had a higher risk of cardiovascular events in relation to systolic/diastolic out-of-office BP (hazard ratios, 1.57 *vs.* 1.22/1.34 *vs.* 1.11; *P*≤0.0340). Similarly, in the age band from 61 to 70 years, cardiovascular risk was also higher in Asians than in Europeans (1.78 *vs.* 1.33/1.50 *vs.* 1.17; *P*≤0.0310).

Discussion

The incidence of cardiovascular mortality and fatal combined with nonfatal cardiovascular complications showed a direct and graded relation with the level of the systolic and diastolic out-of-office BP. The risk associated with out-of-office BP log-linearly increased from levels lower than 110 mm Hg systolic and 65 mm Hg diastolic without any evidence for a threshold. Absolute risk associated with the out-of-office BP increased with age, but relative risk showed an opposite trend, generally increasing from the oldest to youngest age group. These findings were broadly consistent in women and men and across ethnicities.

The observation that from the oldest to the youngest age group absolute risk associated with out-of-office BP decreased, whereas over the same age span relative risk increased, is of great clinical relevance. Indeed, the management of hypertension must be viewed from a lifecourse perspective.[32] Treatment of high BP in young and middle-aged adults prevents subclinical target organ damage and progression to major cardiovascular complications and therefore affects the lifecourse trajectory more than treatment of older people, who are at high absolute risk. With few exceptions, the age-specific risks associated with out-of-office BP were largely consistent in women and men and across people of European and

Asian ancestry. In the age bands from 61 to 70 years and from 71 to 80 years, overall cardiovascular risk associated with out-of-office BP was higher in Asians than in Europeans. Although findings in subgroups might arise by chance, our observations potentially reflect the vast potential for better cardiovascular prevention by antihypertensive treatment in young and middle-aged women,[33] usually thought to be at lower risk than men as well as the possibility of countering the emerging epidemic of coronary artery disease in Asian populations, in whom stroke was traditionally the major complication of hypertension.[34] In fact, a lifecourse approach should not only be applied to hypertension, but to all established modifiable cardiovascular risk factors as well. It should start from childhood and include a more vigorous reinforcement of lifestyle recommendations and a comprehensive management of risk indicators, over and beyond blood pressure, including but not limited to dyslipidemia, impaired glucose tolerance, diabetes mellitus, active and passive exposure to tobacco smoke, early or excessive alcohol consumption, and air pollution. Such policies must pave the way to patient empowerment and a personalized patient-centered care.

Multiple studies established that out-of-office BP, measured by ambulatory[4,5] or home[6] monitoring is a better predictor of adverse health outcomes compared with office BP. In the meta-analysis of one million adults, a 20 mmHg lower usual systolic BP was associated with more than a twofold difference in vascular mortality at ages 40-49 years, and about one-third less vascular mortality at ages of 80-89 years.[1] In our current analysis, hazard ratios of cardiovascular mortality associated with a 20

mmHg increase in out-of-office systolic BP were 1.84 at and below 60 years of age and 1.19 above 80 years. Estimates of relative risk not only depend on the number of events and person-years accruing during a study, but also on the precision with which a risk factor and the outcome under study is measured. In the aforementioned meta-analysis published in 2002,[1] the authors analyzed incident vascular mortality in cohorts recruited from 1949 until 1990 (median 1974; 5th-95th percentile interval, 1959-1987). BP was measured, using standard or random-zero sphygmomanometers with strong preference in some cohorts for recording levels ending in zero; in three studies of US physicians, nurses and health professionals, the participants reported their own BP. In the current study, we applied guideline-endorsed out-of-office BP monitoring which provides more precise estimates of an individual's usual BP.[7-9] Moreover, the increasing deployment of invasive treatment modalities to remediate coronary, cerebrovascular and peripheral arterial conditions drastically reduced cardiovascular mortality. For instance, in a multi-ethnic Asian cohort of 40,623 stroke cases, the 28-day case fatality rate fell by 17.2% from 2006 until 2012.[35] Along similar lines, among 77,211 incident cases of hospitalized acute myocardial infarction followed up in a Scottish study, at all ages (55, 65 and 75 years) and in both sexes, the 30-day case-fatality rate approximately dropped by approximately 50% from 2006 until 2015.[36] These observations possibly explain why the hazard ratios of cardiovascular mortality were lower in our than in Lewington's study.[1]

Diagnostic flow charts for the application of ambulatory and home BP monitoring have been published.[7-9] Both approaches of out-of-office BP measurement are mature, cost-effective,[37] and can be immediately rolled out on a global scale to clinical practice, thereby affecting the lives of millions of people at risk. In low-resource settings, home BP measurement is an alternative for ambulatory BP monitoring. Furthermore, out-of-office BP measurement is required for the diagnosis of masked hypertension; a condition characterized by normal in-office, but elevated out-of-office BP. It has a prevalence of approximately 15% in the general population, and up to 30% in patients with diabetes mellitus.[38] Masked hypertension carries a risk similar to that of combined office and out-of-office hypertension.[38] Similarly, out-of-office BP monitoring enables avoiding needless antihypertensive treatment in patients with an elevated in-office, but normal out-of-office BP, so called white-coat hypertension.[39] In individual patients, daytime and home BP may provide different, albeit still complimentary, information. However, an epidemiological study, such as the current report, does not deal with the management of individual patients, but with risk assessment. We therefore chose to pool daytime and the self-measured home BP as two modalities of out-of-office BP. The rationale was that both types of out-of-office BP measurement are obtained during wakefulness and have the same guideline-endorsed reference thresholds.[7-9] Moreover, the pooled analysis of daytime and home BP was consolidated by similar results for the home, daytime, nighttime and 24-h BP analyzed separately.

The present study describes for the first time the age- sex- and ethnicity-specific risks associated with out-of-office BP. Generalizability is one of its strong points: (i) the available database included information on close to 18,000 individuals, spanning the whole adult age range with equal representation of women and men; (ii) the participants were randomly recruited from populations in 14 countries and three continents; (iii) and the outcomes were collected over a median of 13.2 years of follow-up and encompassed both fatal and nonfatal outcomes validated against the sources available in each country. To our knowledge, only two population studies,[40,41] which complied with the selection criteria of IDACO published in 2007,[10] did not contribute data to the current analysis, because nonfatal events accrued only after the IDACO database had been constructed[40] or because only aggregate data could be made available.[41] Notwithstanding these strengths, our study must also be interpreted within the context of its limitations. First, in all cohorts BP was measured only at baseline. We could therefore not adjust for regression dilution bias.[42] Second, enrolment of the IDACO (Table S1) and IDHOCO (Table S2) population cohorts included in this participant-level meta-analysis started before statins became commonplace in cardiovascular prevention. We also did not have standardized information on the initiation of non-pharmacological and pharmacological cardiovascular preventive measures during follow-up. However, starting antihypertensive or lipid-lowering drugs or health-promoting lifestyle interventions during follow-up would not enhance but rather weaken the associations of study events with out-of-office BP and other risk factors, as measured at baseline. Third,

stroke is the complication of hypertension closest associated with the BP level,[34] but we did not have reliable information on stroke subtypes. Fourth, all fatal and nonfatal study endpoint were adjudicated against the medical records held by doctors and hospitals. However, in view of the different settings of the population studies contributing to IDACO[10] and IDHOCO,[11] the possibility of some misclassification bias in the validation of events cannot be entirely excluded. Finally, Asians were under-represented among our cohorts and we had no information on Blacks of African descent or Blacks born and living in Africa, who generally are more susceptible to the complications of hypertension.[43] We also classified participants enrolled in South America among people of European descent, although there was some degree of indigenous admixture, in particular in the Maracaibo Aging Study.[22]

Perspectives

In this first study of the age- sex- and ethnicity-specific risks of death and cardiovascular complications associated with out-of-office BP, at young age, relative risk was high and absolute risk low, whereas with advancing age relative risk associated with out-of-office BP decreased and absolute risk increased. These observations underscore the need for a lifecourse approach to the management of hypertension. They highlight the necessity to start antihypertensive treatment early in young and middle-aged adults for primary prevention, in particular in women, who compared with men have the same relative risk. In older people, BP lowering treatment should aim at the prevention of disabling complications and extending years lived without disability.

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Conflict of Interest

None of the authors declares a conflict of interest.

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1

Novelty and Significance

What is new?

In a participant-level meta-analysis, we recorded out-of-office blood pressure (BP), either daytime ambulatory (n=12,624) or home (n=5297) BP in 17,921 participants enrolled from 17 populations. Subsequently, mortality and cardiovascular events were recorded. Using multivariable Cox regression, floating absolute risk was computed across four age bands (≤60, 61–70, 71-80 and >80 years) and 5 systolic or 5 diastolic BP categories.

What is relevant?

- Over 236,491 person-years, 3855 people died and 2942 cardiovascular events occurred.
- From 110/65 mm Hg, risk log-linearly increased with higher out-of-office systolic/diastolic BP.
- From ≤60 to >80 years, rates per 1000 person-years increased from 4.4 to 86.3 for all-cause mortality and from 4.1 to 59.8 for cardiovascular events.
- From ≤60 to > 80 years, hazard ratios per 20-mm Hg increment in systolic out-of-office BP decreased from 1.42 (1.19–1.69) to 1.09 (1.05–1.12) for all-cause mortality and from 1.70 (1.51–1.92) to 1.12 for cardiovascular events.
- These age-related trends were similar for out-of-office diastolic BP and were generally consistent in both sexes and across ethnicities.

Summary

Adverse health outcomes were directly associated with out-of-office BP in adults. At young age, absolute risk associated with out-of-office BP was low, but relative risk high, whereas with advancing age relative risk decreased and absolute risk increased. These observations highlight the need of a lifecourse approach for the management of hypertension.

Legends to Figures

Figure 1. Flow chart

Abbreviations: IDACO, International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome (reference 12); IDHOCO International Database of Home Blood Pressure in Relation to Cardiovascular Outcome (reference 13); BP, blood pressure; ABP, ambulatory blood pressure. In 1590 participants, who had both daytime and home BP measured, daytime BP was analyzed as out-of-office BP. Of 12,624 participants with daytime BP, 10,864 had ≥5 nighttime BP readings and were included in the analysis for 24-h and nighttime BP.

Figure 2. Total mortality (A, B) and cardiovascular events (C, D) by
by age-at-risk groups and categories of out-of-office blood pressure.
Point estimates and 95% confidence intervals for the floating absolute risks were plotted along the vertical axis. The size of the squares is proportional to the inverse the variance of each hazard ratio. Risk estimates were stratified by cohort and adjusted for sex, body mass index, serum cholesterol, smoking and drinking, antihypertensive drug treatment and history of diabetes mellitus and cardiovascular disease. The categories plotted along the horizontal axis are <120, 120–129, 130–139, 140–149 and ≥150 mm Hg for systolic blood pressure (SBP) and <70, 70–74, 75–79, 80–84 and ≥85 mm Hg for the diastolic blood pressure (DBP). Log-linear relations were fitted for each age group for out-of-office SBP (A, C), and DBP (B, D).

Figure 3. Hazard ratios for out-of-office blood pressure by four age-at risk groups The Cox models were stratified by cohort and adjusted for sex, age, body mass index, serum cholesterol, smoking and drinking, antihypertensive drug treatment and history of diabetes mellitus and cardiovascular disease. Hazard ratios, given for four age groups, express the risk associated with increments in out-of-office blood pressure (daytime or home) of 20 mm Hg systolic (SBP) or 10 mm Hg diastolic (DBP). Squares representing the point estimates have a size proportional to the inverse of the variance. Horizontal lines denote the 95% confidence interval. *P*-Values are for trend across the four age groups.

Figure 1. Flow chart

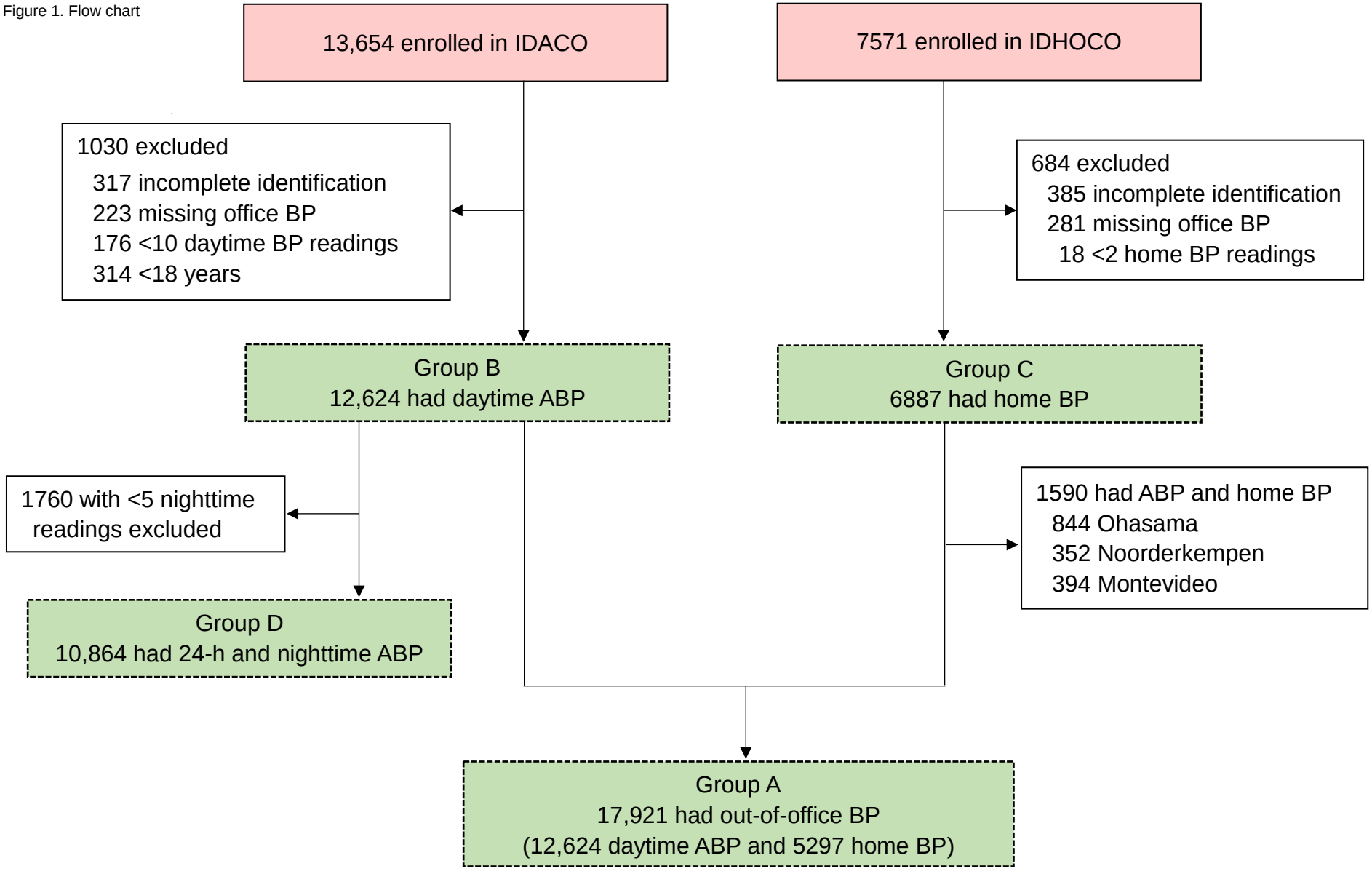

Figure 2. Total mortality (A, B) and cardiovascular events (C, D) by by age-at-risk groups and categories of out-of-office blood pressure.

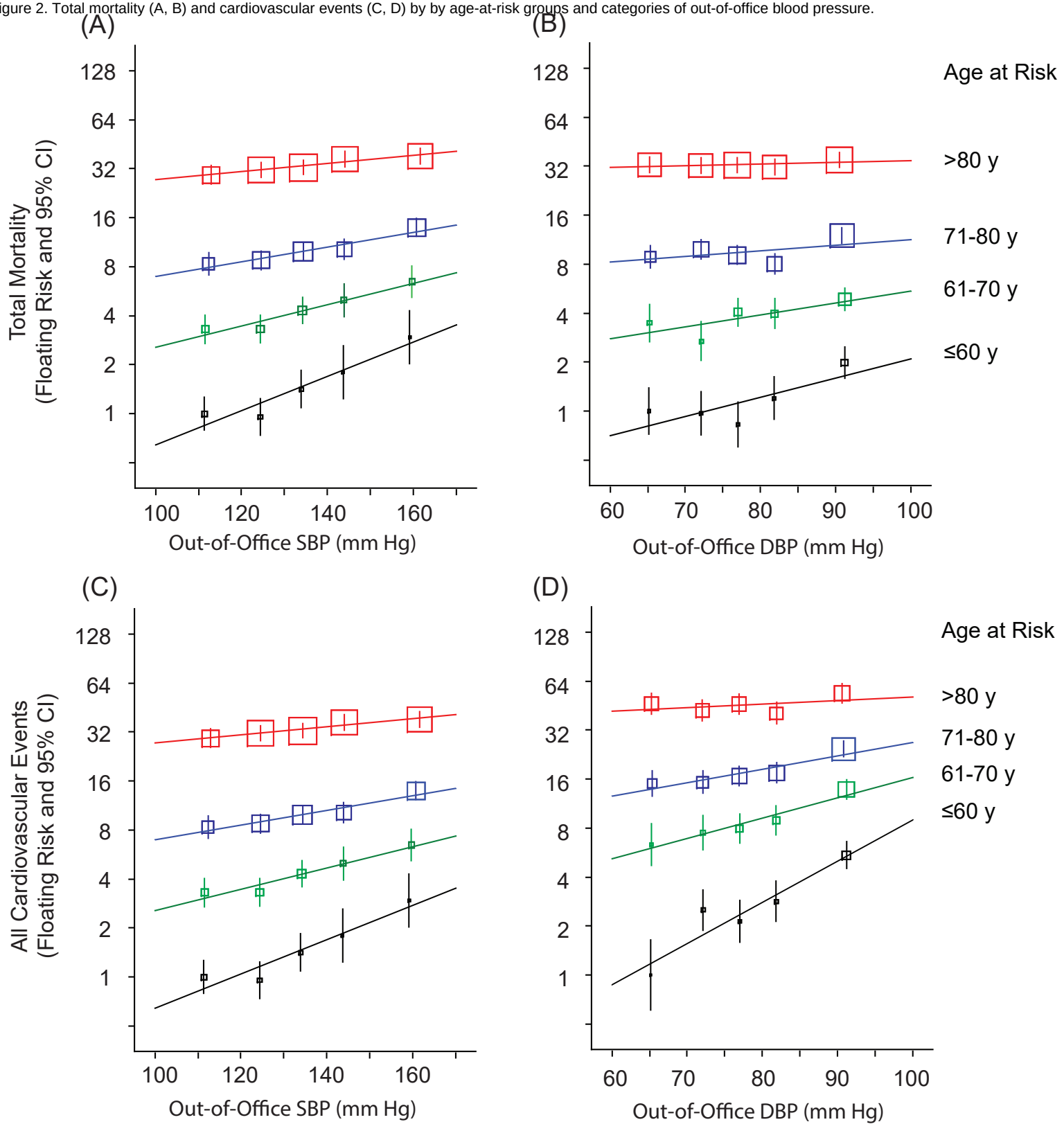

Figure 3. Hazard ratios for out-of-office blood pressure by four age-at risk groups

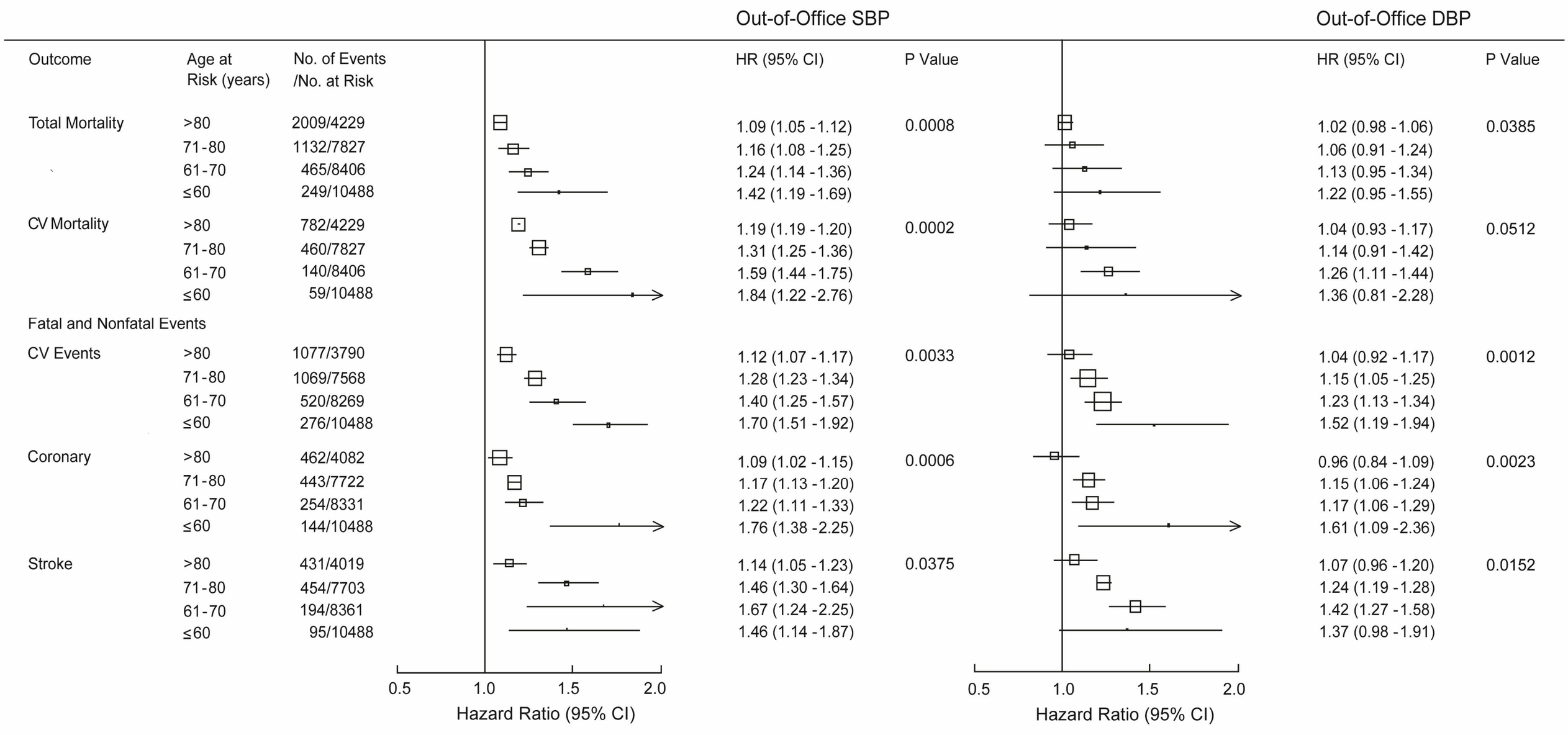

Table 1. Baseline Characteristics of Cohorts by Type of Blood Pressure Measurement (Starts)

Characteristic	Cohorts According to Type of out-of-office BP Measurement		
	Daytime BP (group B)	Home BP (group C)	Out-of-Office BP (group A)
Number of participants (%)			
All participants in category	12,624	6887	17,921
Ethnicity			
Asian	1883 (14.9)	2932 (42.6)	3971 (22.2)
European	8368 (66.3)	3150 (45.7)	11,166 (62.3)
South American	2373 (18.8)	805 (11.7)	2784 (15.5)
Women	6245 (49.5)	3883 (56.4)	9186 (51.3)
Smokers	3484 (27.6)	1395 (20.3)	4580 (25.6)
Drinking alcohol	5946 (47.1)	2941 (42.7)	8343 (46.6)
Obesity			
BMI 25.0–29.9 kg/m^2	4455 (35.3)	2430 (35.3)	6396 (35.7)
BMI ≥30.0 kg/m^2	1794 (14.2)	1019 (14.8)	2632 (14.7)
On antihypertensive drugs	2315 (18.3)	1803 (26.2)	3721 (20.8)
Diabetes mellitus	829 (6.6)	554 (8.0)	1194 (6.7)
History of cardiovascular disease	1350 (10.7)	679 (9.9)	1893 (10.6)
Mean (±SD) of characteristic			
Age (years)	51.7±16.1	59.0±14.1	54.2±16.0
Body mass index (kg/m^2)	25.5±4.4	25.7±4.4	25.6±4.4

Table 1. Baseline Characteristics of Cohorts by Type of Blood Pressure Measurement (continued)

Characteristic	Cohorts According to Type of Out-of-Office BP Measurement		
	Daytime (group B)	Home (group C)	Out-of-Office BP (group A)
Office blood pressure			
Systolic (mm Hg)	131.9±23.1	134.3±20.2	133.1±22.4
Diastolic (mm Hg)	79.7±11.9	79.6±11.6	79.9±11.8
Ambulatory blood pressure			
24-h systolic (mm Hg)	123.9±14.4	…	123.9±14.4
24-h diastolic (mm Hg)	74.0±8.7	…	74.0±8.7
Daytime systolic (mm Hg)	129.3±15.1	…	129.3±15.1
Daytime diastolic (mm Hg)	78.8±9.3	…	78.8±9.3
Nighttime systolic (mm Hg)	112.9±15.6	…	112.9±15.6
Nighttime diastolic (mm Hg)	65.1±9.6	…	65.1±9.6
Home blood pressure			
Systolic (mm Hg)	…	127.3±18.1	129.1±18.6
Diastolic (mm Hg)	…	76.2±9.9	76.9±9.8
Out-of-office blood pressure			
Systolic (mm Hg)	…	…	129.3±16.2
Diastolic (mm Hg)	…	…	78.2±9.5
Biochemical measurements			
Serum cholesterol (mmol/L)	5.56±1.13	5.41±1.07	5.54±1.12
Blood glucose (mmol/L)	5.21±1.46	5.47±1.22	5.28±1.43

In-office BP was the average of two consecutive readings. In 17,921 participants either daytime BP (n=12,624) or home BP (n=5297) was analyzed as out-of-office BP (Group A). Group C includes 6887

participants with home BP. Of 12,624 participants with daytime BP (Group B), 10,864 had ≥5 nighttime BP readings and were included in the means of 24-h and nighttime BP (Group D). Body mass index (BMI) was weight in kilograms divided by the square of height in meters. To convert serum cholesterol from mmol/L to mg/dL multiply by 38.3. Diabetes mellitus was a self-reported diagnosis, a fasting or random blood glucose level of ≥7.0 mmol/L (126 mg/dL) or ≥11.1 mmol/L (200 mg/dL), or use of antidiabetic drugs.

Table 2. Incidence of Events by Baseline Age in Participants with Daytime or Home Blood Pressure

Events	Age (years)				*P* Value
	<60	61-70	71-80	>80	
Number of participants	10,488	3436	3516	481	
Total mortality					
Number of deaths	663	990	1951	251	
Rate (per 1000 person-years)	4.37 (4.04–4.70)	22.3 (21.0–23.7)	51.9 (49.6–54.1)	86.3 (76.1–96.5)	<0.001
Cardiovascular mortality					
Number of deaths	179	337	804	121	
Rate (per 1000 person-years)	1.18 (1.01–1.35)	7.61 (6.80–8.41)	21.4 (19.9–22.8)	41.6 (34.4–48.9)	<0.001
Cardiovascular events					
Number of events	627	772	1377	166	
Rate (per 1000 person-years)	4.22 (3.89–4.55)	18.9 (17.6–20.3)	41.7 (39.5–43.8)	59.8 (51.0–68.7)	<0.001
Coronary events					
Number of events	328	323	588	64	
Rate (per 1000 person-years)	2.19 (1.95–2.42)	7.49 (6.68–8.31)	16.3 (15.0–17.6)	22.1 (16.8–27.5)	<0.001
Stroke					
Number of events	225	342	533	74	
Rate (per 1000 person-years)	1.50 (1.30–1.69)	8.06 (7.21–8.91)	15.0 (13.7–16.2)	26.4 (20.4–32.3)	<0.001

The analysis includes 17,921 study participants. Rates are given with 95% confidence interval. *P* values are for trend.

Hypertension

Online Supplemental Material

Opposing Age-Related Trends in Absolute and Relative Risk of Adverse Health Outcomes Associated with Out-of-Office Blood Pressure

Running Title: Cardiovascular Risk and Out-of-Office Blood Pressure

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Table S1. Recruitment and Follow-Up of IDACO Participants by Cohort

Catchment Area	Sampling Frame	Recruitment		Participation Rate (%)	N° of Participants		Median Follow-Up in Years (5-95% interval)
		Time Period (years)	Invitation		In Database (n=13,654)	Analyzed (n=12,624)	
Ohasama, Iwate, Japan	People aged ≥40 years	1988–1994	Address list	78	1535	1003	22.0 (5.7–26.5)
JingNing, Zhejiang, China	Family-based random sample	2003–2008	All villagers invited	62	895	880	4.0 (3.5–7.6)
Oktyabrsky, Novosibirsk, Russia	Family-based random sample	1999–2001	Address list	68	306	304	16.4 (8.1–17.5)
Niepolomice, Kraków, Poland	Family-based random sample	1999–2008	Address list	54	413	391	13.5 (6.1–14.3)
Gdańsk, Poland	Family-based random sample	2008–2010	Address list	90	215	213	5.6 (4.7–6.7)
Pilsen, Czech Republic	Family-based random sample	2000–2001	Address list	82	174	174	14.1 (13.8–14.4)
Padova, Italy	Population-based sample of women and men≥18 years	1999–2007	Address list	73	314	314	13.3 (12.6–14.5)
Noordkempen, Belgium	Family-based random sample	1985–2008	Address list	78	2904	2580	18.1 (8.6–25.8)
Uppsala, Sweden	Men aged ≥50 years	1991–1995	Population census	73	1143	1135	15.1 (3.5–22.2)
Copenhagen County, Denmark	Stratified random sample of women and men aged 30, 40, 50 and 60 years	1993–1997	Population registry	83	2311	2296	16.3 (5.2–17.3)
Dublin, Ireland	Bank employees working at branches across Ireland	1989–1991	All invited	14	981	961	17.6 (16.5–18.2)
Maracaibo,	City resident aged	1998–2008	Population	71	604	601	8.1

Venezuela	≥55 years		census					(1.7–13.7)
Montevideo, Uruguay	Age-stratified random sample	1995–1998	Members of a health insurance organization	78	1859	1772		9.0 (4.2–10.7)

The European Project on Genes in Hypertension included participants recruited in Novosibirsk, Kraków, Gdańsk, Pilsen and Padova. Participants from Padova were recruited in Mirano in the province of Venice and in Torrebelvicino and Valli del Pasubio in the province of Vicenza. Participation rate refers to the percentage of people invited at enrolment, who provided written informed consent and were enrolled.

Table S2. Recruitment and Follow-Up of IDHOCO Participants by Cohort

Catchment Area	Sampling Frame	Recruitment		Participation Rate (%)	N° of Participants		Median Follow-Up in Years (5-95% interval)
		Time Period (years)	Invitation		In Database (n=7571)	Analyzed (n=6887)	
Ohasama, Iwate, Japan	People aged ≥35 years	1988–1995	Address list	80	2758	2115	20.7 (3.6-27.5)
Tsurugaya, Japan	All residents of Tsurugaya aged ≥ 70 years	2002	Address list	43	836	817	5.5 (2.3–5.6)
Noordkempen, Belgium	Family-based random sample	2012-2013	Address list	78	411	411	2.9 (2.1–3.7)
Didima, Greece	Residents of Didima aged ≥18 years	1997	Address list	76	665	665	18.9 (4.2–19.4)
Finnish National Sample	Two-stage cluster sample of people aged 45–74 years	2000–2001	Population registry	48	2075	2074	13.2 (6.6–13.3)
Buenos Aires, Argentina	Hospital Italiano	2008-2010	Referrals for health check-up	100	426	406	3.7 (1.7–4.5)
Montevideo, Uruguay	Age-stratified random sample	1996–1998	Members of a health insurance organization	34	400	399	8.9 (5.7–10.6)

Participation rate refers to the percentage of people invited at enrolment, who provided written informed consent and were enrolled.

Table S3. 24-H Ambulatory Blood Pressure Monitoring by IDACO Cohort

Study Cohorts	N° of People (n=10,864)	Monitoring Device	Minutes between Readings		N° of Readings over 24 Hours					
			Day	Night	Programmed	Median	P5	P25	P75	P95
Ohasama, Iwate, Japan	1001	ABP-630, Nippon Colin	30	30	48	46	36	42	48	50
JingNing, Zhejiang, China	875	90207, SpaceLabs	20	30-45	59–65	56	48	55	57	62
Oktyabrsky, Novosibirsk, Russia	300	90202, SpaceLabs	15	30	76	71	56	65	75	78
Niepolomice, Kraków, Poland	389	90202, SpaceLabs	15	30	76	74	54	63	77	79
Gdańsk, Poland	212	TM-2430, A&D	20	45	65	62	50	59	64	64
Pilsen, Czech Republic	165	90202, SpaceLabs	20	45	65	75	56	71	80	82
Padova, Italy	314	90202, SpaceLabs	15	30	76	76	64	74	77	78
Noordkempen, Belgium	1412	90202, SpaceLabs	20	40	55	53	38	41	56	58
Uppsala, Sweden	1097	Accutracker II	20–30	20–60	41–72	66	44	53	75	85
Copenhagen County, Denmark	2142	TM-2421, A&D	15	30	80	80	68	80	81	83
Dublin, Ireland	930	90202 and 90207, Spacelabs	30	30	48	46	39	44	48	49
Maracaibo, Venezuela	589	90207, SpaceLabs	15	30	80	67	53	61	71	77
Montevideo, Uruguay	1438	90207, SpaceLabs	20	40	60	67	53	61	71	77

The TM-2421 and TM-2430 monitors implement both an auscultatory and an oscillometric technique. However, only oscillometric readings were used for analysis. All devices passed validation. Participants with fewer than five nighttime readings were excluded (n=1760).

Table S4. Home Blood Pressure Measurement by IDHOCO Cohort

Study Cohorts	N° of People (n=6887)	Monitoring			N° of Home Blood Pressure Readings					
		Device	N° of Days	Times per Day	Planned	Median	P5	P25	P75	P95
Ohasama, Iwate, Japan	2115	Omron HEM-401C	28	2 (M, E)	56	52	17	40	55	59
Tsurugaya, Japan	817	Omron HEM-722C	30	1 (M)	30	13	3	5	26	33
Noordkempen, Belgium	411	Omron HEM-705CP	7	2 (M, E)	42	42	24	37	45	54
Didima, Greece	665	Omron HEM-705CP	3	2 (M, E)	12	12	11	12	12	12
Finnish National Sample	2074	Omron HEM-722C	7	2 (M, E)	28	28	16	28	28	28
Buenos Aires, Argentina	406	Omron HEM-705CP	4	3 (M, A, E)	24	24	20	24	26	28
Montevideo, Uruguay	399	SpaceLabs 90207	1	2 (M, E)	2	2	2	2	2	2

Abbreviations: M, morning; A, afternoon; E, evening. All devices passed validation.

Table S5. Number of Daytime and Nighttime Blood Pressure Readings by IDACO Cohort

Study Cohorts	Daytime							Nighttime						
	N° of People (n=12,624)	Planned Readings	Median	P5	P25	P75	P95	N° of People (n=10,864)	Planned Readings	Median	P5	P25	P75	P95
Ohasama, Iwate, Japan	1003	20	19	14	17	21	22	1001	12	11	8	11	12	12
Jing-Ning, Zhejiang, China	880	30	30	21	29	31	32	875	8–12	8	7	8	8	12
Oktyabrsky, Novosibirsk, Russia	304	40	37	26	33	40	42	300	12	12	11	12	12	12
Niepolomice, Kraków, Poland	391	40	39	26	32	41	43	389	12	12	8	10	12	12
Gdańsk, Poland	213	30	29	21	27	30	31	212	12	12	9	12	12	12
Pilsen, Czech Republic	174	40	37	25	34	40	42	165	12	11	9	11	12	12
Padova, Italy	314	40	40	32	39	41	59	314	12	13	12	13	13	25
Noordkempen, Belgium	2580	30	30	19	26	34	40	1412	8	8	6	7	9	9
Uppsala, Sweden	1135	20–30	30	20	25	33	38	1097	6–18	8	6	7	18	21
Copenhagen County, Denmark	2296	40	40	29	39	41	43	2142	12	13	11	13	13	13
Dublin, Ireland	961	20	19	15	18	20	21	930	12	12	10	11	12	13
Maracaibo, Venezuela	601	40	32	21	28	35	39	589	12	12	9	11	12	12
Montevideo, Uruguay	1772	30	18	11	16	20	21	1438	9	6	6	6	7	7

Daytime was the interval from 10:00 h to 20:00 h in Europeans and South Americans, and from 08:00 h to 18:00 h in Asians. The corresponding nighttime intervals ranged from midnight to 06:00 h and from 22:00 h to 04:00 h, respectively. Participants with fewer than five nighttime readings were excluded from the nighttime statistics (n=1760).

Table S6. Incidence of Events by Type of Out-of-Office Blood Pressure Measurement

Events	Daytime (group B)	Home (group C)	Daytime or Home (group A)
Number of participants	12,624	6887	17,921
Total mortality			
Number of deaths	2754	1478	3855
Rate (per 1000 person-years)	16.1 (15.5–16.7)	17.0 (16.2–17.9)	16.3 (15.8–16.8)
Cardiovascular mortality			
Number of deaths	1047	503	1441
Rate (per 1000 person-years)	6.11 (5.74–6.48)	5.80 (5.29–6.31)	6.09 (5.78–6.41)
Cardiovascular events			
Number of events	2072	1072	2942
Rate (per 1000 person-years)	12.7 (12.2–13.2)	13.0 (12.2–13.8)	13.1 (12.6–13.5)
Cardiac events			
Number of events	1427	569	1924
Rate (per 1000 person-years)	8.59 (8.14–9.03)	6.69 (6.14–7.23)	8.37 (8.00–8.75)
Coronary events			
Number of events	972	372	1303
Rate (per 1000 person-years)	5.79 (5.42–6.15)	4.34 (3.90–4.78)	5.61 (5.31–5.92)
Stroke			
Number of events	783	527	1174
Rate (per 1000 person-years)	4.66 (4.34–4.99)	6.28 (5.75–6.82)	5.08 (4.79–5.37)

The group definitions are presented in Figure 1. Rates are given with 95% confidence interval.

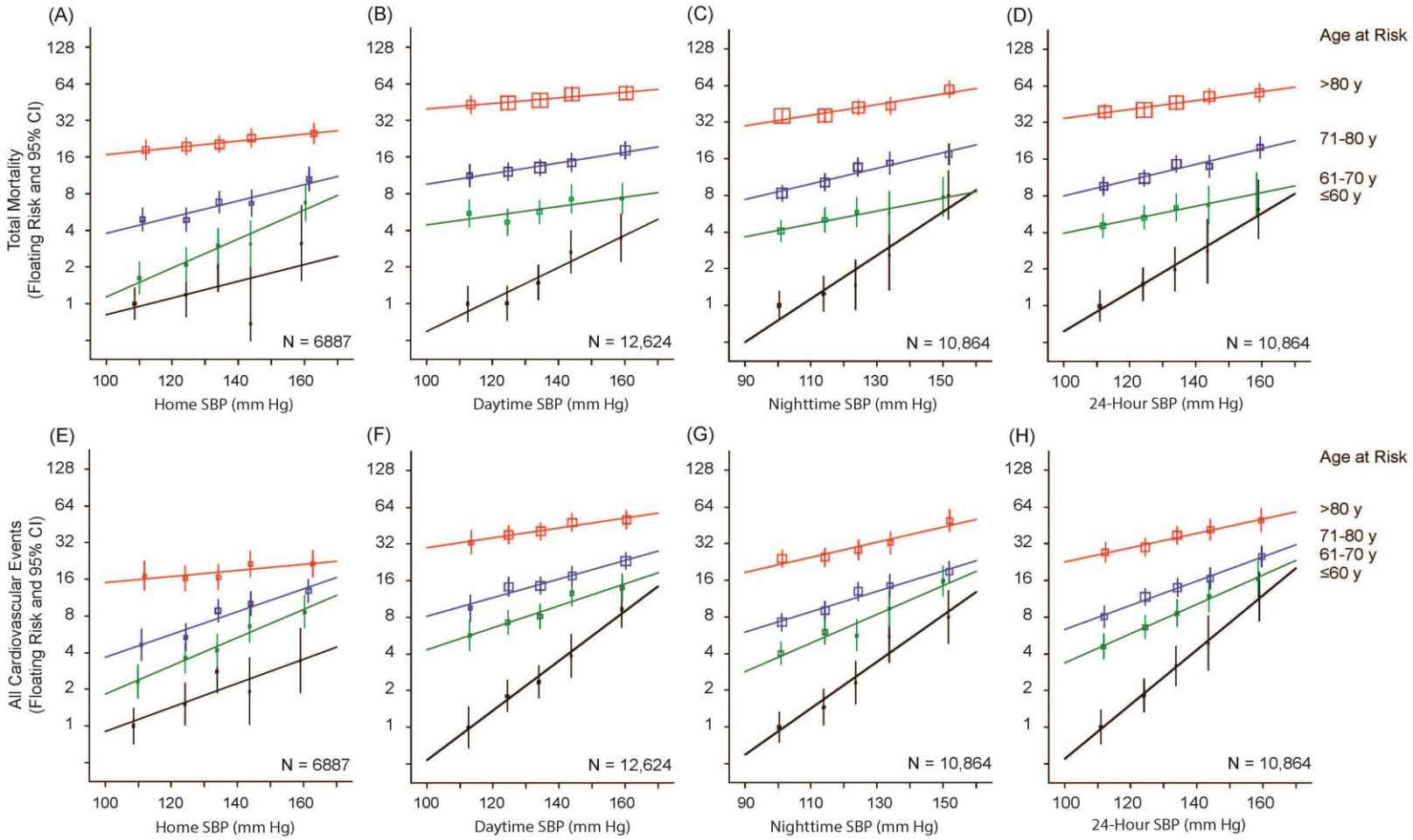

Figure S1. Total mortality and cardiovascular events by age-at-risk groups and categories of home, daytime, nighttime, and 24-h systolic blood pressure.

Point estimates and 95% confidence intervals (CI) for the floating absolute risks were plotted along the vertical axis. The size of the squares is proportional to the inverse the variance of each hazard ratio. Risk estimates were stratified by cohort and adjusted for sex, age, body mass index, total serum cholesterol, smoking and drinking, antihypertensive drug treatment and history of diabetes mellitus and cardiovascular disease. The categories of systolic blood pressure (SBP) plotted along the horizontal axis are <120, 120–129, 130–139, 140–149 and ≥150 mm Hg for home, daytime, and the 24-h SBP (A, B, D, E, F, H), and <110, 110–119, 120–129, 130–139 and ≥140 mm Hg for nighttime SBP (C, G). Log-linear relations were fitted for each age group.

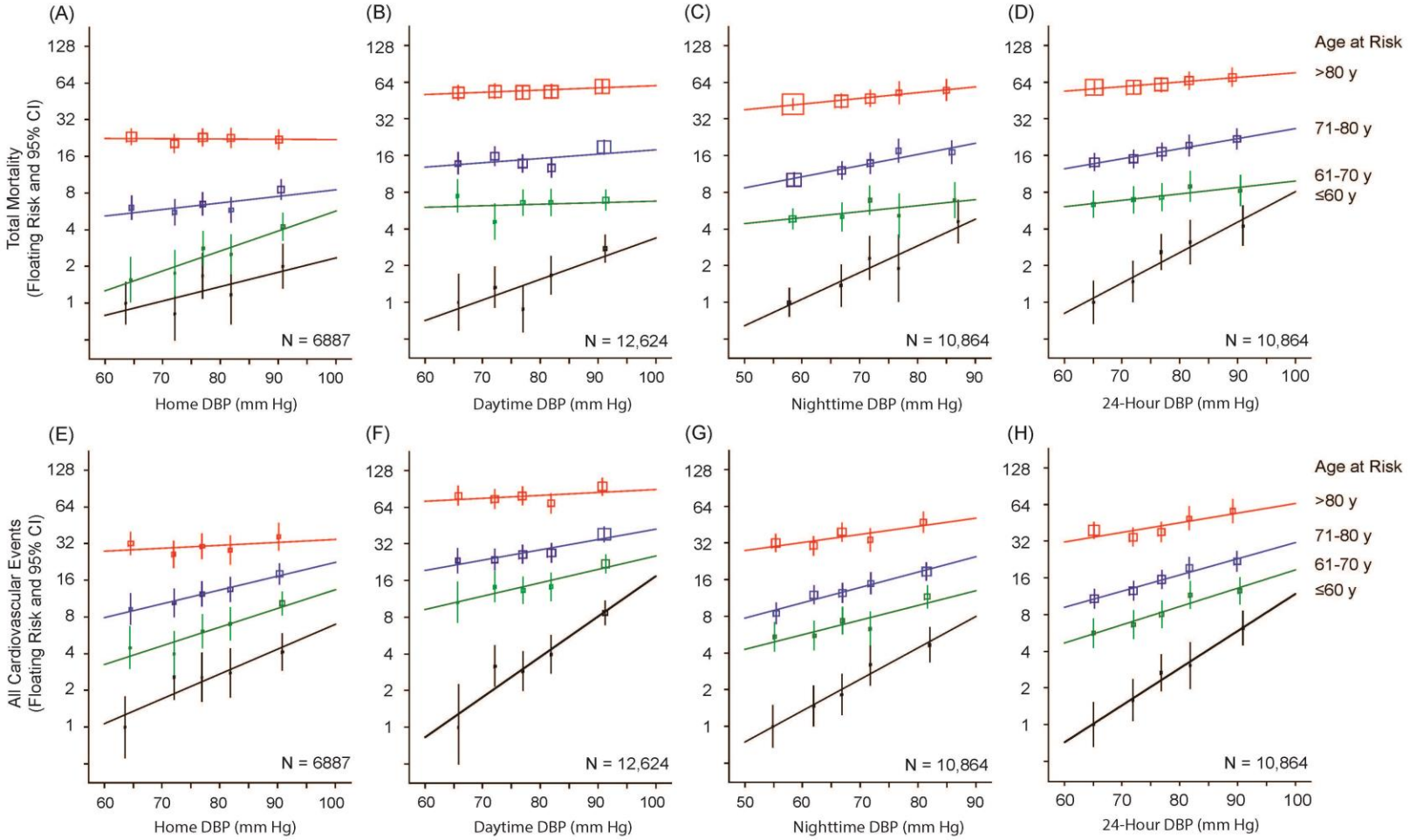

Figure S2. Total mortality and cardiovascular events by age-at-risk groups and categories of home, daytime, nighttime, and 24-h diastolic blood pressure.

Point estimates and 95% confidence intervals (CI) for the floating absolute risks were plotted along the vertical axis. The size of the squares is proportional to the inverse the variance of each hazard ratio. Risk estimates were stratified by cohort and adjusted for sex, age, body mass index, serum cholesterol, smoking and drinking, antihypertensive drug treatment and history of diabetes mellitus and cardiovascular disease. The categories of diastolic blood pressure (DBP) plotted along the horizontal axis are <70, 70–74, 75–79, 80–84 and ≥85 mm Hg for home, daytime, and 24-h DBP (A, B, D, E, F, H) and <60, 60–64, 65–69, 70–74 and ≥75 mm Hg for nighttime DBP (C, G). Log-linear relations were fitted for each age group.

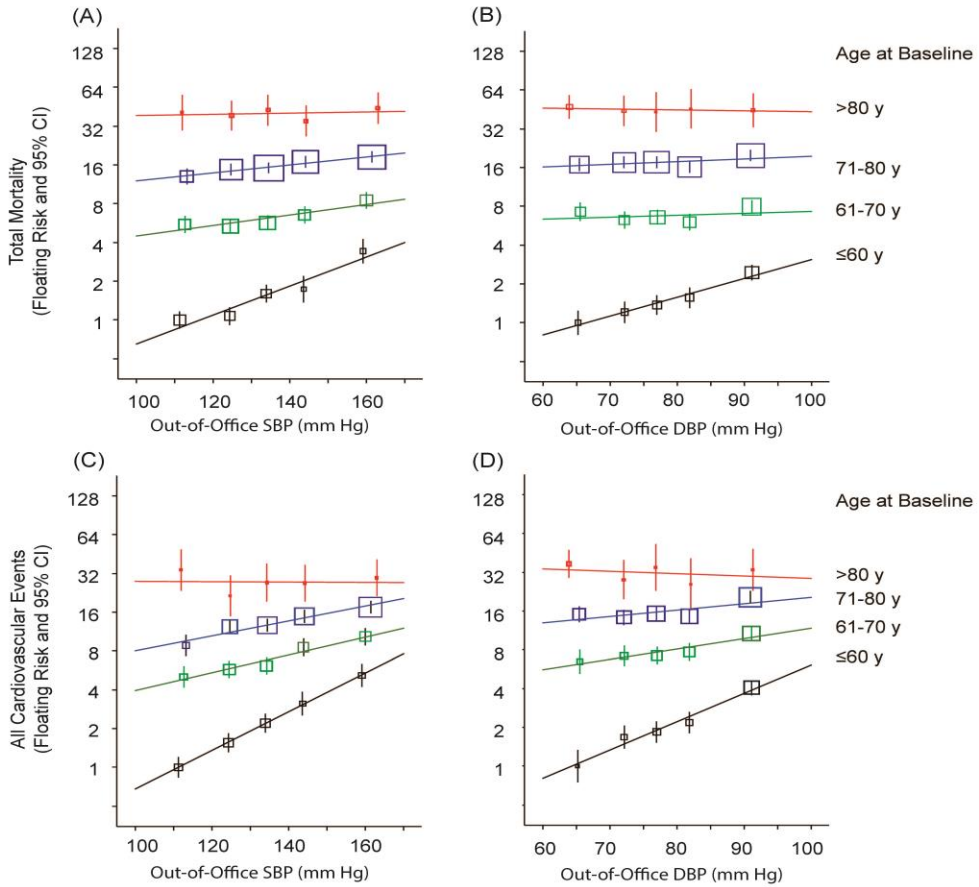

Figure S3. Total mortality (A, B) and cardiovascular events (C, D) by baseline-age groups and categories of out-of-office blood pressure.

Point estimates and 95% confidence intervals for the floating absolute risks were plotted along the vertical axis. The size of the squares is proportional to the inverse the variance of each hazard ratio. Risk estimates were stratified by cohort and adjusted for sex, body mass index, serum cholesterol, smoking and drinking, antihypertensive drug treatment and history of diabetes mellitus and cardiovascular disease. The categories plotted along the horizontal axis are <120, 120–129, 130–139, 140–149 and ≥150 mm Hg for systolic blood pressure (SBP) and <70, 70–74, 75–79, 80–84 and ≥85 mm Hg for the diastolic blood pressure (DBP). Log-linear relations were fitted for each age group for out-of-office SBP (A, C), and DBP (B, D).

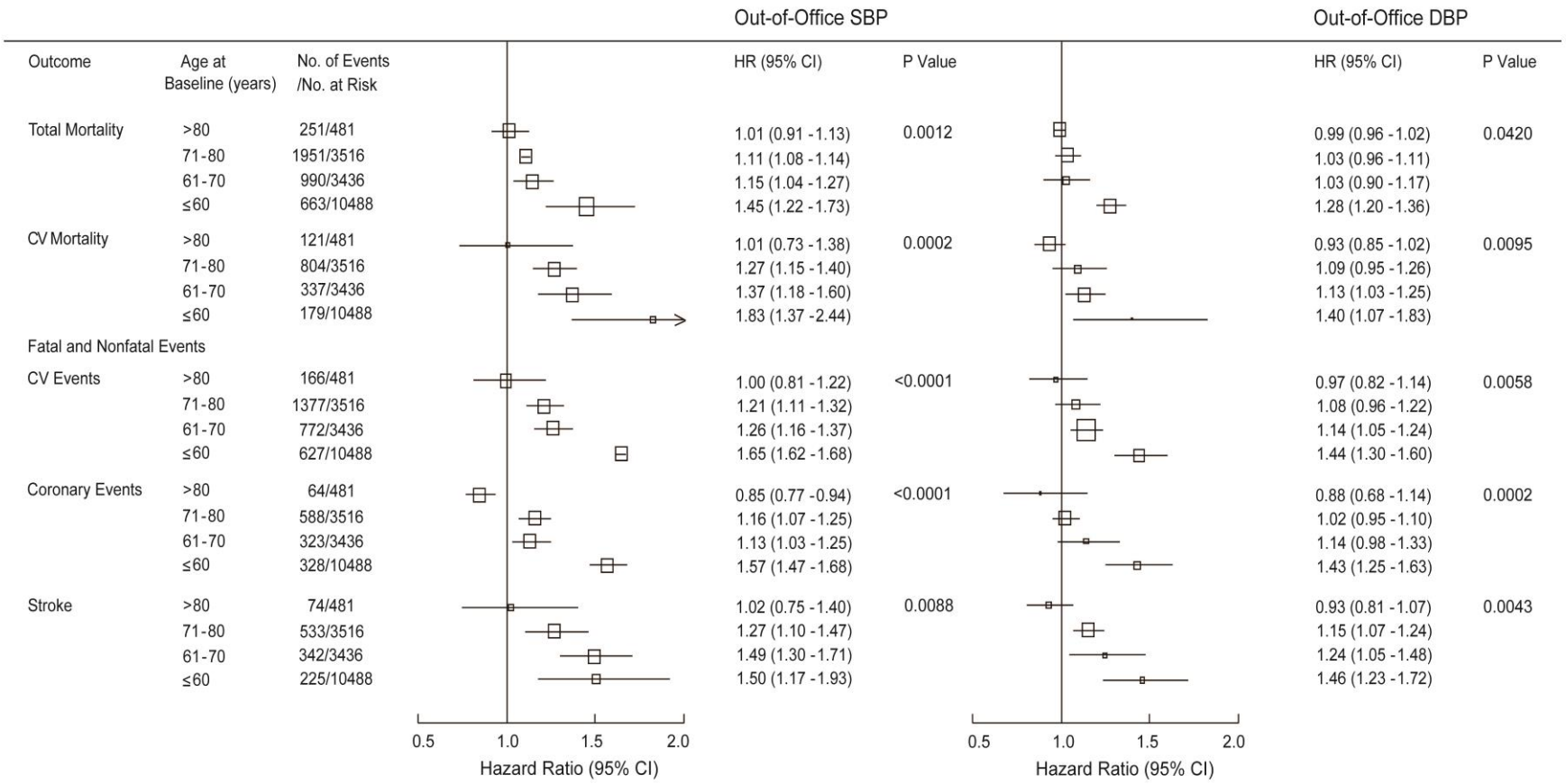

Figure S4. Hazard ratios for out-of-office blood pressure by baseline-age groups.

The Cox models were stratified by cohort and adjusted for sex, age, body mass index, serum cholesterol, smoking and drinking, antihypertensive drug treatment and history of diabetes mellitus and cardiovascular disease. Hazard ratios, given for four age groups, express the risk associated with increments in out-of-office blood pressure (daytime or home) of 20 mm Hg systolic (SBP) or 10 mm Hg diastolic (DBP). Squares representing the point estimates have a size proportional to the inverse of the variance. Horizontal lines denote the 95% confidence interval. *P*-Values are for trend across the four age groups.

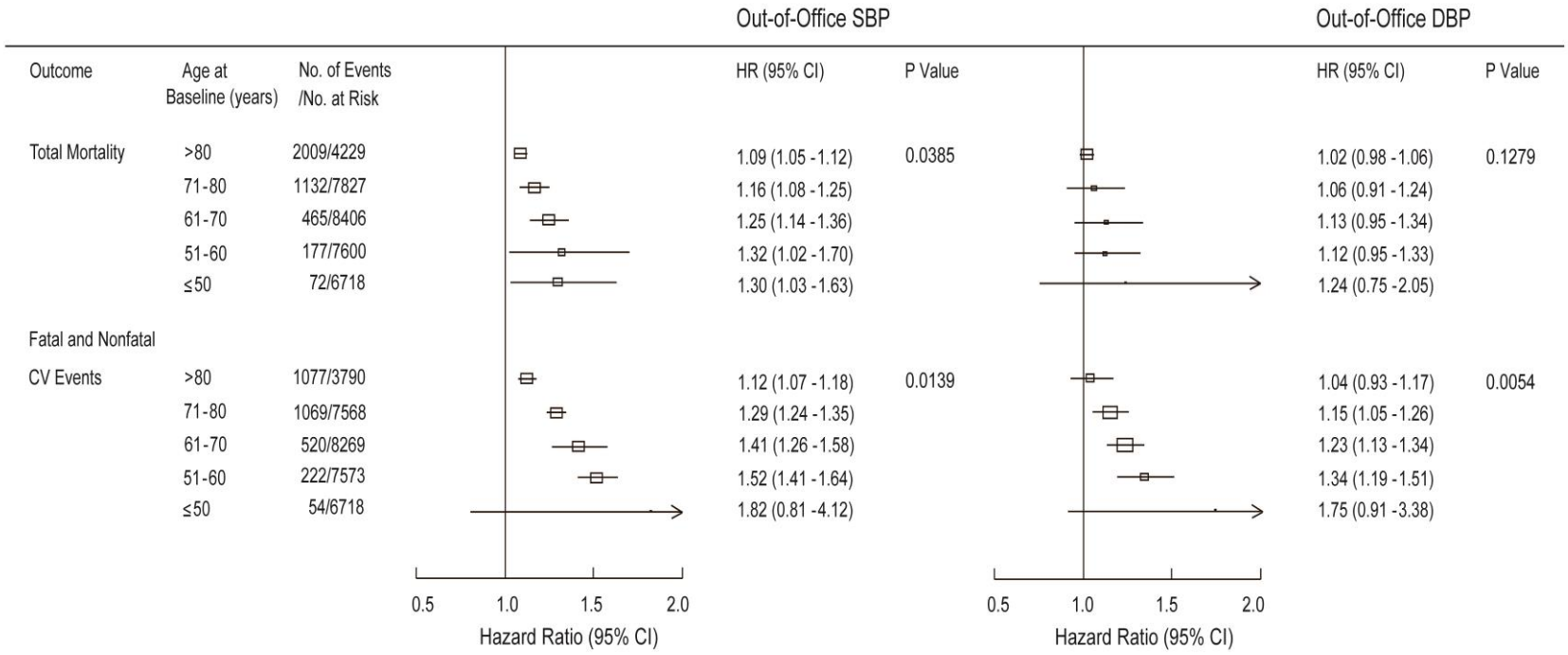

Figure S5. Hazard ratios relating total mortality and all cardiovascular events to out-of-office blood pressure by five age-at-risk groups.

The Cox models were stratified by cohort and adjusted for sex, age, body mass index, serum cholesterol, smoking and drinking, antihypertensive drug treatment and history of diabetes mellitus and cardiovascular disease. Hazard ratios, given for five age-at-risk groups, express the risk associated with increments in out-of-office blood pressure (daytime or home) of 20 mm Hg systolic (SBP) or 10 mm Hg diastolic (DBP). Squares representing the point estimates have a size proportional to the inverse of the variance. Horizontal lines denote the 95% confidence interval. P-Values are for trend across the five age groups.

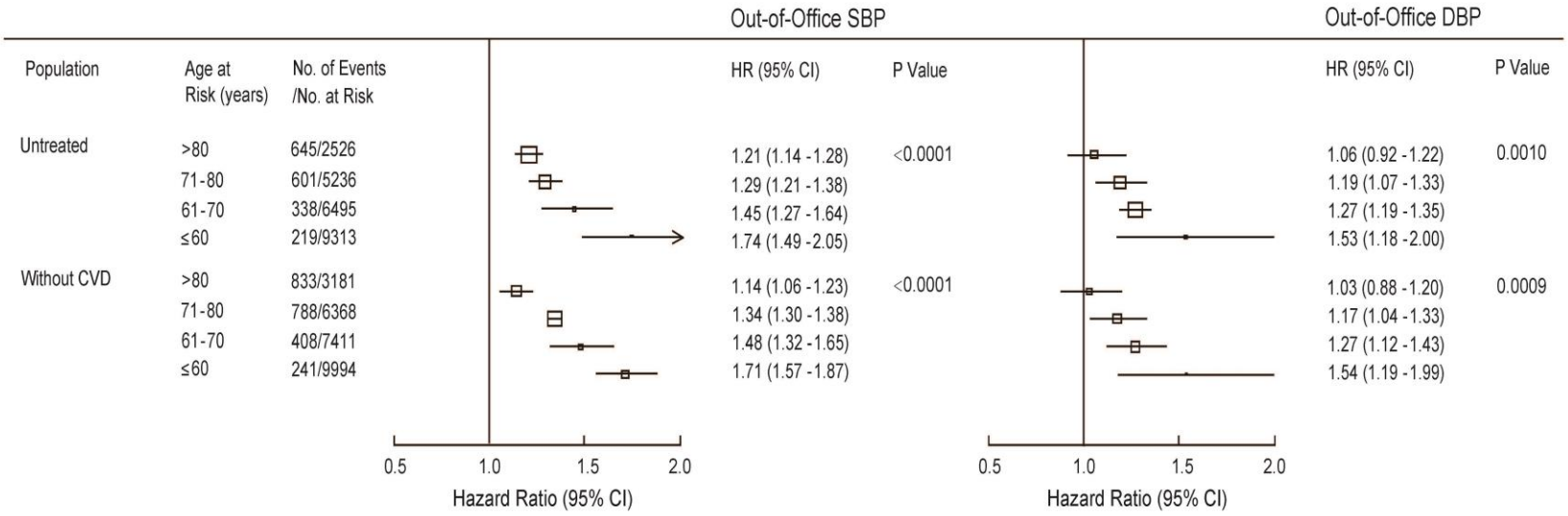

Figure S6. Hazard ratios relating all fatal and nonfatal cardiovascular events to out-of-office systolic and diastolic blood pressure in participants untreated (n=14,161) or free of cardiovascular disease (n=16,026) at baseline.

The Cox models were stratified by cohort and adjusted for sex, age, body mass index, serum cholesterol, smoking and drinking, antihypertensive drug treatment and history of diabetes mellitus and cardiovascular disease. Hazard ratios, given for four age groups, express the risk associated with increments in out-of-office blood pressure (daytime or home) of 20 mm Hg systolic (SBP) or 10 mm Hg diastolic (DBP). Squares representing the point estimates have a size proportional to the inverse of the variance. Horizontal lines denote the 95% confidence interval. *P*-Values are for trend across the four age groups.

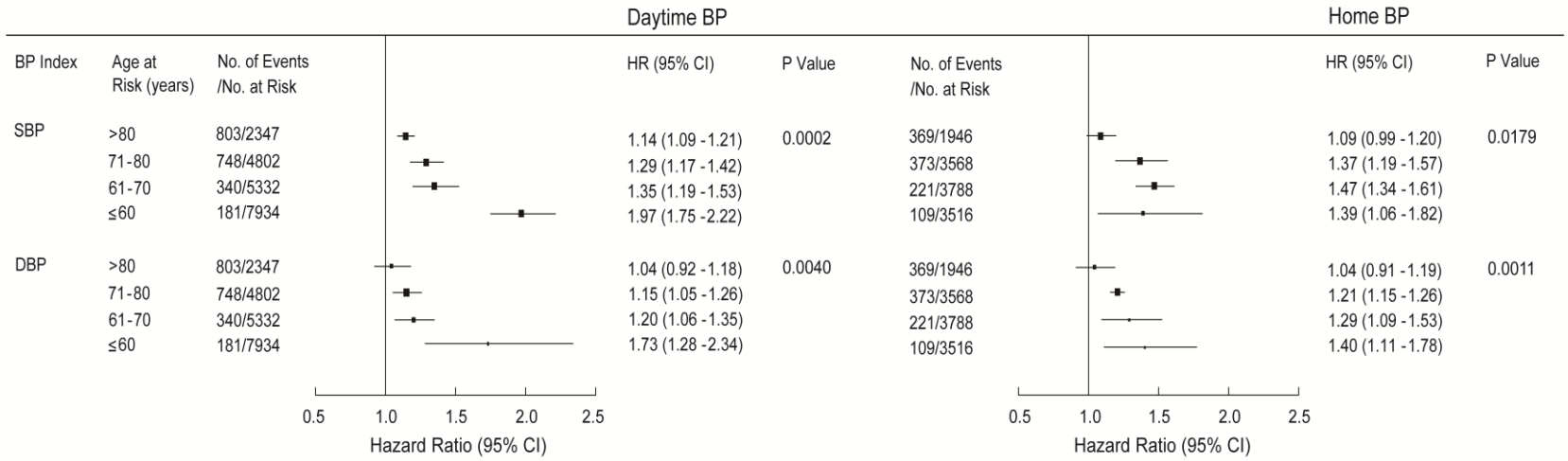

Figure S7. Hazard ratios relating all fatal and nonfatal cardiovascular events to daytime ambulatory and home systolic and diastolic blood pressure.

The Cox models were stratified by cohort and adjusted for sex, age, body mass index, serum cholesterol, smoking and drinking, antihypertensive drug treatment and history of diabetes mellitus and cardiovascular disease. Hazard ratios, given for four age groups, express the risk associated with increments in daytime ambulatory (n=12,624) or home (n=6887) of 20 mm Hg systolic (SBP) or 10 mm Hg diastolic (DBP). Squares representing the point estimates have a size proportional to the inverse of the variance. Horizontal lines denote the 95% confidence interval. *P*-Values are for trend across the four age groups.

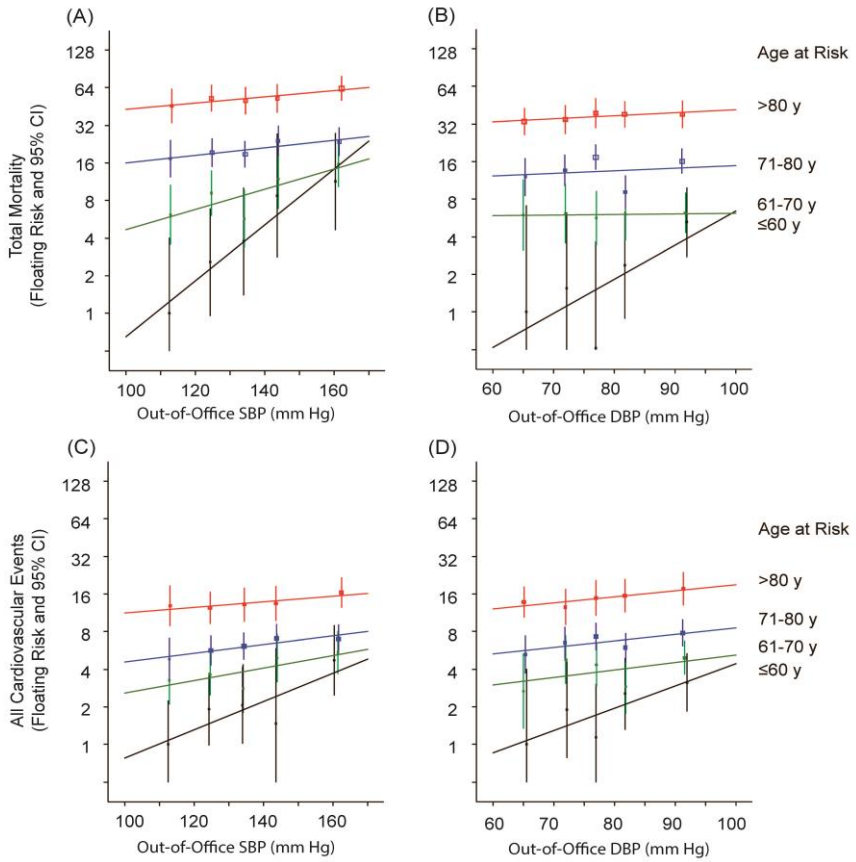

Figure S8. Total mortality (A, B) and cardiovascular events (C, D) by age-at-risk groups and categories of out-of-office blood pressure in 1893 participants with history of cardiovascular disease.

Point estimates and 95% confidence intervals for the floating absolute risks were plotted along the vertical axis. The size of the squares is proportional to the inverse the variance of each hazard ratio. Risk estimates were stratified by cohort and adjusted for sex, body mass index, serum cholesterol, smoking and drinking, antihypertensive drug treatment and history of diabetes mellitus and cardiovascular disease. The categories plotted along the horizontal axis are <120, 120–129, 130–139, 140–149 and ≥150 mm Hg for systolic blood pressure (SBP) and <70, 70–74, 75–79, 80–84 and ≥85 mm Hg for the diastolic blood pressure (DBP). Log-linear relations were fitted for each age group for out-of-office SBP (A, C), and DBP (B, D).

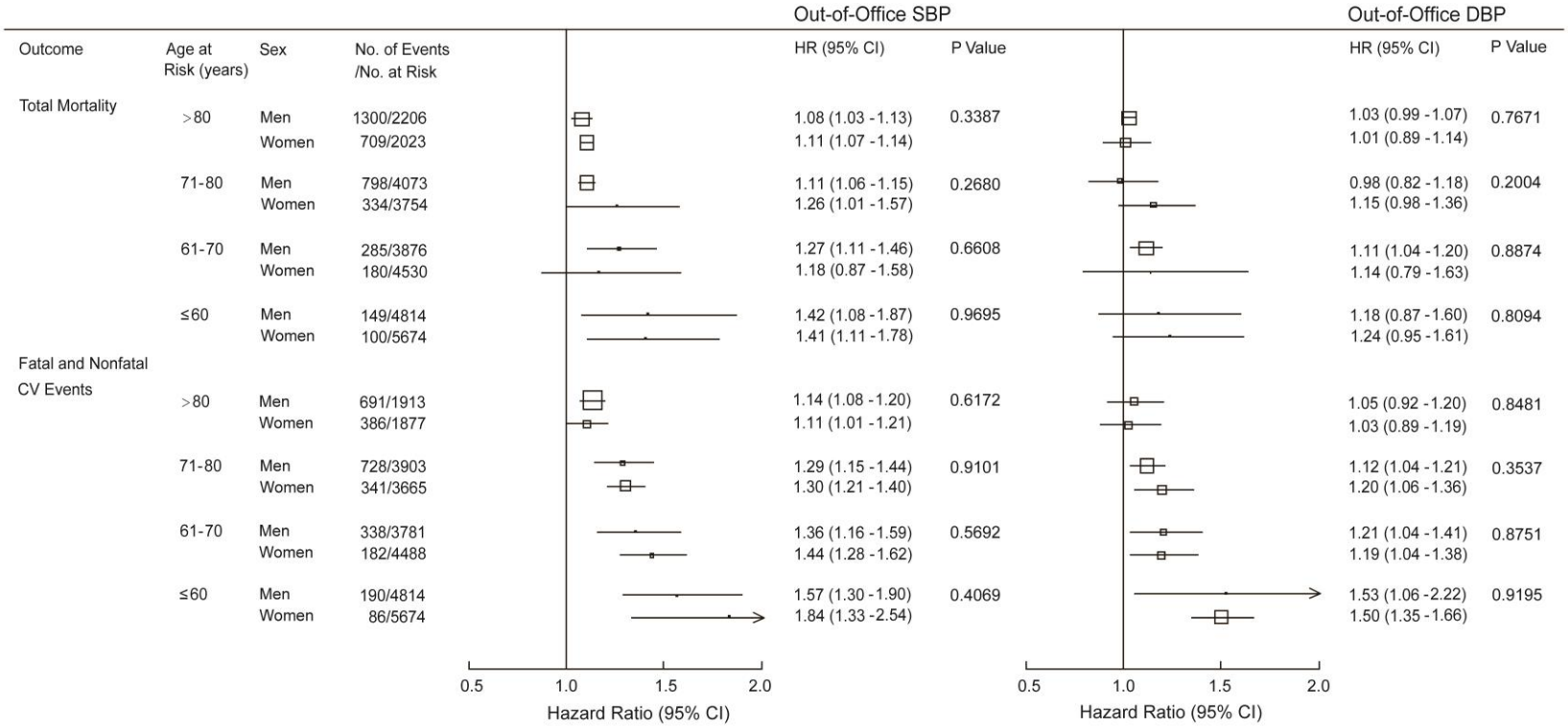

Figure S9. Age- and sex-specific hazard ratios relating total mortality and cardiovascular events to out-of-office systolic and diastolic blood pressure.

The Cox models were stratified by cohort and adjusted for sex, age, body mass index, serum cholesterol, smoking and drinking, antihypertensive drug treatment and history of diabetes mellitus and cardiovascular disease. Hazard ratios, given for four age-at-risk groups, express the risk associated with increments in out-of-office blood pressure (daytime or home) of 20 mm Hg systolic (SBP) or 10 mm Hg diastolic (DBP). Squares representing the point estimates have a size proportional to the inverse of the variance. Horizontal lines denote the 95% confidence interval. P-Values are for the sex differences within each age band.

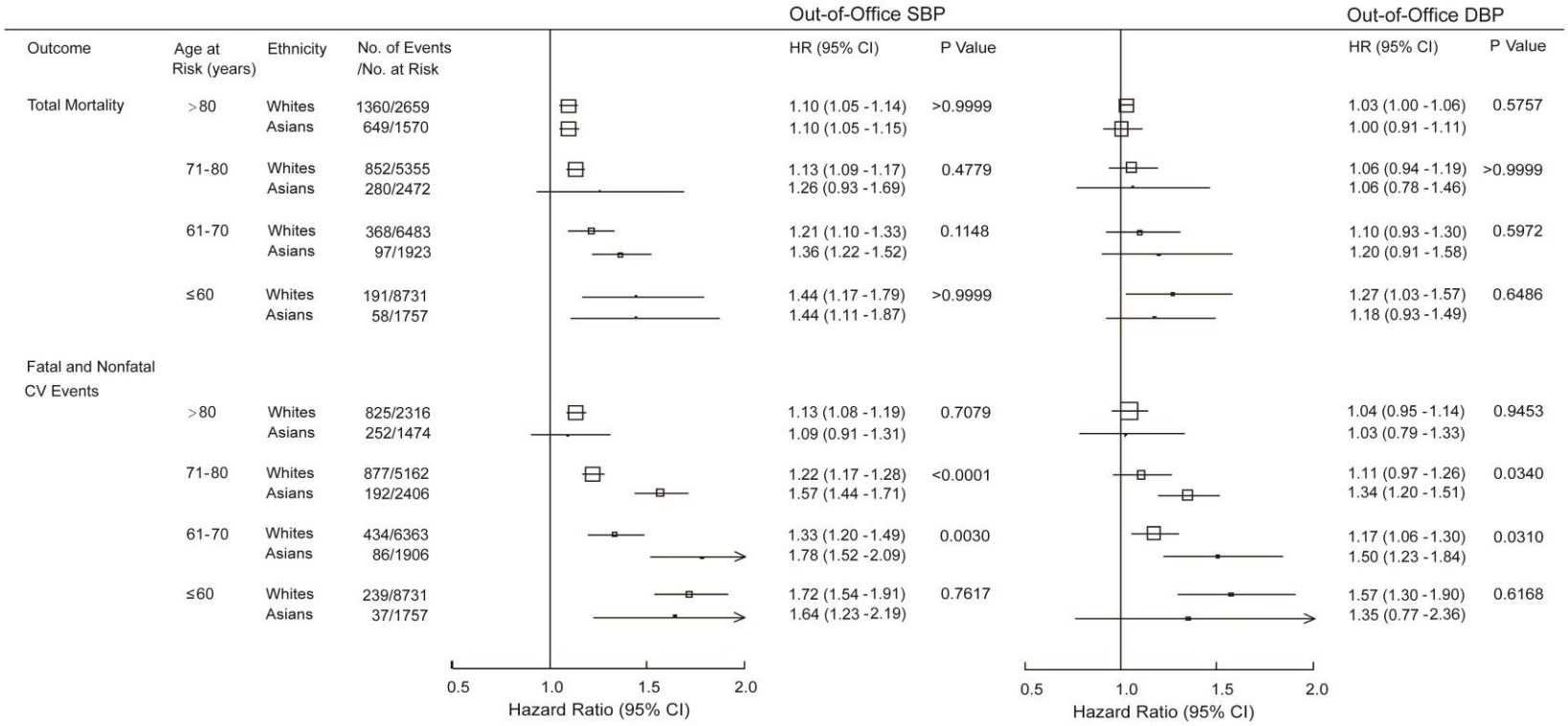

Figure S10. Age- and ethnicity-specific hazard ratios relating total mortality and cardiovascular events to out-of-office systolic and diastolic blood pressure**.**

The Cox models were stratified by cohort and adjusted for sex, age, body mass index, serum cholesterol, smoking and drinking, antihypertensive drug treatment and history of diabetes mellitus and cardiovascular disease. Hazard ratios, given for four age-at-risk groups, express the risk associated with increments in out-of-office blood pressure (daytime or home) of 20 mm Hg systolic (SBP) or 10 mm Hg diastolic (DBP). Squares representing the point estimates have a size proportional to the inverse of the variance. Horizontal lines denote the 95% confidence interval. P-Values are for the ethnic difference within each age band.