Systolic blood pressure and vascular disease in men aged 65 and over: the Health In Men Study (HIMS)

Short title: *Blood pressure and vascular disease in older men*

Ben Lacey, MBChB, DPhil, FFPH [1,2,3]	ben.lacey@ndph.ox.ac.uk
Jonathan Golledge, MChir, FRACS [4,5]	jonathan.golledge@jcu.edu.au
Bu B. Yeap, MBBS, FRACP, PhD [2,6]	bu.yeap@uwa.edu.au
Sarah Lewington, DPhil [3]	sarah.lewington@ctsu.ox.ac.uk
Kieran A. McCaul, MPH, PhD [1,2]	kieran.mccaul@uwa.edu.au
Paul E. Norman, DS, FRACS[7]	paul.norman@uwa.edu.au
Leon Flicker, MBBS, PhD, FRACP [1,2,8]	leon.flicker@uwa.edu.au
Osvaldo P. Almeida, MD, PhD [1,2,9]	osvaldo.almeida@uwa.edu.au
Graeme J. Hankey, MD, FRACP, FAHA [2,10]	graeme.hankey@uwa.edu.au

[1]Western Australian Centre for Health & Ageing, Centre for Medical Research, University of Western Australia, Australia

[2]School of Medicine and Pharmacology, University of Western Australia;

[3]Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, University of Oxford, United Kingdom

[4]Queensland Research Centre for Peripheral Vascular Disease, College of Medicine and Dentistry, James Cook University, Australia

[5]The Department of Vascular and Endovascular Surgery, The Townsville Hospital, Townsville, Australia

[6]Department of Endocrinology and Diabetes, Fiona Stanley and Fremantle Hospitals, Perth, Australia

[7]School of Surgery, University of Western Australia, Australia

[8]Department of Geriatric Medicine, Royal Perth Hospital, Perth, Australia;

[9]School of Psychiatry and Clinical Neurosciences, University of Western Australia, Australia

[10]Department of Neurology, Sir Charles Gairdner Hospital, Perth, Australia

Total word count (including references, tables and figures etc.): 5994

Word count of abstract: 224

Total number of figures and tables: 6

Date: 25th January 2017

Address of Correspondence:

Dr Ben Lacey, WA Centre for Health & Ageing (M573), University of Western Australia, 35 Stirling Highway, Crawley, WA 6009, Australia

Tel: (+61) 8 9224 2855

Fax: (+61) 8 9224 8009

E-mail: ben.lacey@ndph.ox.ac.uk

Abstract

There is uncertainty about the relation between blood pressure and vascular disease at older age. We assessed the association of systolic blood pressure (SBP) and major vascular events in a prospective cohort study of 7564 men aged 65-94 years, recruited in 1996-99 from the general population in Perth, Western Australia. SBP was measured at baseline and again at resurvey in 2001-4. Participants were monitored for fatal and non-fatal vascular events. To limit the effect of reverse causality, analyses were restricted to men without previous vascular disease at baseline. Hazard ratios were estimated by Cox regression with adjustment for age and education (further adjustment did not materially change the associations). During a mean follow-up of 11 years, there were 1557 major vascular events. Continuous log-linear associations were found between usual SBP and risk of major vascular events throughout the SBP range examined (145-170 mmHg). Overall, 10 mmHg higher usual SBP was associated with about 20% higher risk of major vascular events (hazard ratio 19% [95%CI 13%-26%]; mean age at event 80 years). There was evidence of positive associations with both ischaemic heart disease and stroke, and effect modification by age with shallower associations at older ages. Even at 85-94 years, however, there was evidence of a positive association: 10 mmHg higher usual SBP was associated with 14% (95%CI 1%-30%) higher risk of major vascular events.

Key words: blood pressure, hypertension, vascular diseases, elderly, epidemiology

Introduction

Vascular disease, including ischaemic heart disease and stroke, is a leading cause of death and disability worldwide.[1] Blood pressure is an established risk factor for vascular disease but few prospective cohort studies have specifically investigated the effects of raised blood pressure at older age, and particularly in the very elderly (such as those aged 85 years and over).

Meta-analyses of prospective studies have described strong positive associations between blood pressure and vascular disease in middle age, but much shallower associations in later life.[2-4] These meta-analyses have been limited, however, in their ability to assess the effect of raised blood pressure on vascular outcomes in the elderly: they have not been able to conduct the detailed assessment for confounding and reverse causality that a single study allows. Furthermore, clinical trials of blood pressure-lowering medication have tended to have few very elderly participants, so there is some uncertainty about the effect of blood pressure-lowering medication on ischaemic heart disease and stroke in this patient group. [5-7]

We report the association between systolic blood pressure (SBP) and incidence of major vascular events in an Australian population-based prospective cohort study of men aged 65 years or over. We investigate whether the association varies by age (including findings for those aged 85-94 years) and by type of vascular event, and assess which blood pressure index (systolic, diastolic or some combination of these) is the most predictive of major vascular events in this age group.

Methods

Study design and participants

Men recruited into the Health In Men Study (HIMS) were originally part of a population-based randomised trial of screening for abdominal aortic aneurysm conducted in Perth, Western Australia. The trial methods have been described in detail elsewhere.[8] In brief, all men resident in Perth and projected to be aged 65-79 years at the mid-point of screening, were randomly selected from the electoral roll in 1996-99 and invited to undergo ultrasound screening of their abdominal aorta. Of 19 352 potentially eligible men, 12 203 attended a screening visit. At this visit, they completed a questionnaire on sociodemographic factors, lifestyle and medical history. Physical measurements were also made, including blood pressure, height and weight. Screened men received a letter (together with a copy for their general practitioner) with information on the size of their aorta. The letter did not attempt to influence the clinical management of the general practitioner and no further intervention was made as part of the trial. All screened men were recruited into the HIMS cohort. Participants were monitored for deaths and hospital admissions using the Western Australian Data Linkage System.[9]

For the present study, we excluded men with missing information on key variables (n=54); those with extreme SBP values (<80 or >250 mmHg; n=6); those with a history of heart disease (n=3419) or stroke (n=1735) at baseline, to limit the effect of reverse causality; and, those with an abdominal aortic aneurysm (≥30 mm in diameter) identified at screening (n=875), as these individuals are likely to have

received medical intervention to address their risk of a major vascular event. The remaining 7564 men contributed person-years until the censoring date (Dec 31, 2010), first major vascular event or death.

Ethics approval for the study was obtained from the Human Research Ethic Committee of the University of Western Australia, and all men provided written informed consent to participate.

Blood pressure measures at baseline and resurvey

At baseline, SBP was measured twice on the upper arm of each participant (after they remained seated for at least 5 minutes) using an automated sphygmomanometer and recorded to the nearest 2 mmHg. The mean of the two SBP measurements was used in all analyses. SBP was measured again at resurvey in 2001-04 (5.8 years, on average, after the baseline survey) using the same procedures. All participants of the baseline survey were invited to the resurvey and 4263 attended. Participants excluded at baseline in the main analyses of the present study (see Statistical analysis) were also excluded from analyses of resurvey blood pressure, leaving 2862 men. Resurvey blood pressure was used to correct hazard ratios for regression dilution bias.[10] Rosner's regression method was used to calculate the regression dilution ratio for SBP, the ratio being equal to the slope of the regression line between baseline and resurvey blood pressures.[11, 12]

Outcome measures

The Western Australian Data Linkage System collects information on deaths and

inpatient hospital admissions throughout Western Australia, with records from 1970 onwards. The underlying cause of death and hospital discharge diagnoses were coded to the International Classification of Diseases (ICD) 9-10. The primary outcome in this study was first major vascular event. This was defined as first hospitalisation or death from ischaemic heart disease (non-fatal myocardial infarction [ICD-10: I21-23] or death from ischaemic heart disease [I20-25]), stroke (non-fatal stroke or stroke death [I60-61, I63-64, H34.1]) or other vascular death (vascular deaths [I60-99] except from stroke or ischaemic heart disease) (see Table S1 in the online-only Data Supplement for details).

Statistical analysis

Cox regression models, with attained age at the underlying time variable, were used to calculate hazard ratios for first major vascular event versus SBP. Analyses were adjusted for age at risk and highest level of education (some primary, some high school, completed high school, completed university). Assessment was made for further confounding by region of birth (Australia, Europe, Mediterranean, other), smoking (never smoker, ex-smoker, current smoker), quantity of weekly alcohol intake (none, 1-7, 8-14, ≥15 units), weekly vigorous activity (yes, no), BMI (< 22.5, 22.5–24.9, 25.0–27.4, 27.5–29.9, ≥ 30.0 kg/m^2), self-reported diabetes (yes, no) and use of cholesterol medication (yes, no). There were no missing data on age, highest level of education or blood pressure; missing values of other variables formed a separate category in each variable.

In continuous analyses, log risk was regressed on SBP and hazard ratios were given per 10 mmHg higher usual SBP. In categorical analyses, which were used to

assess the shape of the association, men were divided into five groups according to baseline blood pressure <140, 140-<150, 150-<160, 160-<170, ≥170 mmHg SBP. Hazard ratios for major vascular events were calculated relative to the lowest blood pressure group and plotted against usual SBP in these baseline-defined categories. The 95% confidence intervals about the hazard ratios in the categorical analyses were calculated using the variance of the log risk.[13] The absolute risk of higher blood pressure was illustrated by multiplying the hazard ratios by a common factor to make the inverse-variance weighted average of the hazard ratios match the annual incidence of major vascular events in this cohort (the annual incidence rates were calculated as the unweighted average of the component five-year incidence rates; see Table S2).[14]

The association of usual SBP and first major vascular event was reported by age at risk (65-74, 75-84 and 85-94 years) and by type of major vascular event (ischaemic heart disease, stroke and other vascular deaths). Age-specific associations were also reported for ischaemic heart disease and stroke, but not for other vascular deaths as there were too few events in this category. Chi-squared tests for heterogeneity and, where appropriate, tests for trend were applied to hazard ratios to assess for effect modification. Tests for trend by age used mean age at event in each age group. Sensitivity analyses, to assess for reverse causality from pre-clinical vascular disease at baseline, were conducted by excluding the first two years of follow-up.

Using measurements of blood pressure recorded at baseline only (ie, not correcting for regression dilution bias), the relative importance of different blood

pressure indices was assessed by comparing hazard ratios for a 1-SD difference in each index and by likelihood ratio X^2 tests. Hazard ratio (adjusted for age at risk and education) were calculated for the association of each blood pressure index to incidence of major vascular events. The likelihood ratio X^2 statistic of each of these regression models was compared to the X^2 statistic of the same models excluding the given blood pressure index; the difference indicating the improvement of goodness of fit between models (more predictive blood pressure indices would tend to have a greater effect on X^2 values).[2, 15] The X^2 values were expressed as a proportion of the X^2 values for SBP. A range of blood pressure indices were compared: SBP, DBP, mid blood pressure (1/2 SBP +1/2 DBP), mean arterial pressure (1/3 SBP + 2/3 DBP), and pulse pressure (SBP-DBP).

Analyses were performed using Stata (v12.0) and figures were plotted using R (v3.0).

Role of funding sources

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Following exclusions, there were 7654 men aged 65-83 years at baseline without a history of vascular disease. Their mean age at recruitment was 73 (SD 4) years

and they were followed up for 11 (SD 4) years, on average, to Dec 31, 2010. During that period, 1557 incident major vascular events occurred: 833 ischaemic heart disease events, 551 strokes and 173 other vascular deaths. The mean age at event was 80 (SD 6) years.

Mean SBP at baseline was 158.1 (SD 21) mmHg and ranged from 156.1 mmHg at age 65-69 years to 161.7 mmHg at age 80-83 years. Table 1 shows the characteristics of participants by tertile of baseline SBP. Both age and BMI were positively associated with SBP. Those in the lowest SBP tertile also had a lower proportion of self-reported diabetics and weekly drinkers than higher SBP tertiles. There was a slight negative association between baseline SBP and the proportion of men undertaking weekly vigorous exercise, but no evidence of an association with smoking. Overall, 28% of men reported taking blood pressure-lowering medication and this proportion increased from 18% in the lowest SBP tertile to 38% in the highest SBP tertile.

The characteristics of resurveyed men differed slightly from the characteristics of the participants surveyed at baseline (Table S3). Those resurveyed tended to be better educated (resurvey 21% vs baseline 14%), were slightly less likely to smoke (11% vs 8%), a higher proportion undertook weekly vigorous exercise (34% vs 27%) and a slightly lower proportion had diabetes (7% vs 10%). The association between SBP at baseline and resurvey was linear (Figure 1) and the regression dilution ratio was 0.42. There was no evidence of confounding of this relationship by age or education, or effect modification by age; neither was it materially

affected by excluding participants taking blood pressure-lowering medication at baseline or resurvey (Tables S4 and S5).

At age 65-94 years, there was a positive 'log-linear' association between usual SBP and incidence of major vascular events, throughout the range of blood pressure measurements examined (145-170 mmHg usual SBP) (Table 2, Figure 2; Table S6). Adjusting for age and education (and correcting for regression dilution bias), 10 mmHg higher usual SBP was associated with about 20% higher risk of major vascular events (hazard ratio [HR] 1.19 [95% CI 1.13-1.26]). Progressive adjustment for a set of major potential confounders did not materially affect the strength of the association, and neither did the exclusion of events during the first two years of follow-up or of those taking blood pressure-lowering medication at baseline (Table S7).

There were strong, positive associations at all ages between usual SBP and incidence of major vascular events (Table 2). The proportional increase in risk was somewhat greater at younger than at older ages, but even at very old there was evidence of a positive association (age 85-94 years HR 1.14 [95% CI 1.01-1.30]). As the incidence of major vascular events was so much greater at older age, however, the annual absolute difference in incidence associated with a given difference in usual SBP was greater at older than younger ages (Figure S1).

Ischaemic heart disease accounted for over half (54%) the number of major vascular events and stroke for about a third (35%). Both diseases were positively, and roughly log-linearly, associated with usual SBP throughout the blood pressure

range (Figure S1). The strength of the association for ischaemic heart disease (HR 1.19 [95% CI 1.10-1.28]) was much the same as stroke (1.16 [1.05-1.27]) (Table 2). There was some evidence, however, that the proportional increase in risk was greater at younger than older ages for both ischaemic heart disease and stroke, with this effect being more pronounced for stroke than ischaemic heart disease (Table 3).

There was no significant heterogeneity (p=0.4) across hazard ratios by subtype of stroke event, although there was limited power to detect any difference: at ages 65-94 years, hazard ratio per 10 mmHg higher SBP were 1.26 (95% CI 1.11-1.44) for ischaemic stroke, 1.08 (0.85-1.36) for intracerebral haemorrhage and 1.05 (0.88-1.24) for other or unspecified stroke (Table S8). There was a strong association with other vascular deaths combined (HR 1.35 [95% CI 1.14-1.59]) but too few deaths in this category (n=173) to stratify further this association by disease group (Table S9). Also, there was no evidence that blood pressure had an effect on risk of non-vascular death (Table S10).

There was no strong evidence that the hazard ratios for the associations of major vascular events with blood pressure (using baseline measures of blood pressure only) differed between blood pressure indices (Table 4). However, when comparing X^2 values for Cox regression models with and without each blood pressure index, SBP was found to improve the goodness of fit more than other blood pressure indices: relative to SBP, the X^2 values were 90% for mid blood pressure, 79% for mean arterial pressure, 72% for pulse pressure and 41% for diastolic blood pressure (Table S11). The prospective

associations of usual DBP with major vascular events are given in the online-only Data Supplement (Tables S12 and S13).

Discussion

In this cohort of older men, we undertook a detailed assessment the relation between usual SBP and incidence of major vascular disease. We found that at age 65-94 years, the proportional difference in risk of major vascular events associated with a given absolute difference in usual SBP was constant throughout the blood pressure range examined (145-170 mmHg usual SBP). There was evidence of a positive association with both ischaemic heart disease and stroke, and effect modification by age with shallower associations at older ages. However, even at very old age (85-94 years) there was strong evidence of a positive association. For predicting the incidence of major vascular events from a single blood pressure measurement at baseline, SBP was found to more predictive than other blood pressure indices.

The overall findings for ischaemic heart disease are broadly consistent with those of large meta-analyses of prospective.[2-4] The Prospective Studies Collaboration meta-analysis of 61 prospective cohort studies (conducted mainly in the West) found that, at ages 75-84 years, 10 mmHg higher usual SBP was associated with 26% (95% CI 25%-28%) increased risk of ischaemic heart disease. [4] In the Asia Pacific Cohort Studies Collaboration meta-analysis of 37 prospective cohort studies (conducted mainly in East Asia but with about a fifth of participants from Australia and New Zealand), 10 mmHg higher usual SBP was associated with

21% (12%-31%) higher risk of ischaemic heart disease at ages 75-84 years. [4] Our findings from the present study indicate that this increased risk for vascular events extends to men aged 85-94 years.

For stroke, the Prospective Studies Collaboration found that, at ages 75-84 years, 10 mmHg higher usual SBP was associated with 25% (21%-31%) increased risk of ischaemic stroke and 31% (24%-39%) increased risk of intracerebral haemorrhage.[2, 4] Similar findings were reported by the Asia Pacific Cohort Studies Collaboration for this same age group, with 10 mmHg higher SBP associated with 33% (24%-42%) increased risk of ischaemic stroke and 26% (19%-34%) increased risk of intracerebral haemorrhage.[3, 4] Most strokes in the present study were ischaemic, and the strength of this association was consistent with the aforementioned studies.

Few meta-analyses of clinical trials have described the effect of blood pressure-lowering medication on cardiovascular events in older adults.[6, 7, 16] A meta-analysis of 31 clinical trials using individual participant data reported that at ≥65 years of age (mean age at entry was 72 years), each 5 mmHg reduction in SBP was associated with a 9.1% (95% CI 3.6%-14.3%) reduction in risk of major cardiovascular events.[6] The strength of this association is equivalent to 21% (95% CI 8%-36%) higher risk per 10 mmHg higher SBP, consistent with the overall association in the present study. The association by type of major vascular event or at older ages was not reported. An observational study, assembled using electronic health records of 1.25 million patients registered with primary care practices in the UK, described shallower age-specific associations than the

present study for myocardial infarction and stroke.[17] The reason for this is unclear and may reflect the lack of a formal resurvey of blood pressure in this study.

The Hypertension in the Very Elderly Trial (HYVET), for which the results were published subsequently to the aforementioned meta-analysis, addressed the effect of a blood pressure-lowering medication in those aged 80 years and older (mean age at entry was 84 years).[18] At median follow-up of 2 years, blood pressure had been reduced by 15.0 mmHg SBP and 6.1 mmHg DBP, on average, in the active-treatment group relative to the control group (the target blood pressure was 150 mmHg SBP and 80 mmHg DBP). The effect on risk of cardiovascular death in this trial was in keeping with the overall finding of the present study for major vascular events: standardised to 10 mmHg higher SBP, the association was equivalent to 19% (95% CI -1%-41%) increased risk of cardiovascular death. There was strong evidence of an adverse effect of higher blood pressure on death from any cause in this trial (there was a 17% [95% CI 3%-33%] increased risk per 10 mmHg SBP), but substantial uncertainty about the effect for incident (fatal and non-fatal) myocardial infarction (24% [-30%-23%]) and incident stroke (27% [-1%-61%]). Thus, the benefits of blood-pressure lowering therapy on specific cardiovascular diseases is less well established at age 80 and over than at younger ages.

The present study found that when using a single blood pressure measurement, SBP was statistically more predictive of major vascular events overall than diastolic blood pressure or other blood pressure indices (as assessed using likelihood ratio X^2 tests), although the magnitude of this was small. This is in contrast to some studies conducted in younger populations which find mid blood

pressure or mean arterial pressure to be more predictive than either SBP or DBP alone.[2] This finding might reflect the weaker predictive ability of DBP in this older population.

The present study had a number of major strengths: blood pressure was measured using standardised procedures; the resurvey of blood pressure meant it was possible to assess for regression to the mean and correct analyses for regression dilution bias; the baseline survey allowed assessment for confounding by a broad range of factors; and, the established data linkage system, used to identify causes of death and hospitalisations in study participants, is likely to have high diagnostic accuracy and case-ascertainment of major vascular events (although it was not possible to assess formally losses to follow-up).[19, 20]

The study would have benefited from a greater number of events, as this would have allowed the strength of associations to have been estimated more precisely. Another limitation is that men who attended the baseline survey may have subsequently made efforts to address their risk factors for vascular disease. However, excluding men from the analyses who were identified with abdominal aortic aneurysm at baseline is likely to have limited this effect. There was also some evidence that those resurveyed differed somewhat from those not resurveyed, given they had a lower prevalence of a number of vascular risk factors than those surveyed at baseline overall. There is, however, no evidence to suggest the regression dilution ratios for SBP would have been affected by these differences. Also, recruiting only men meant that the overall associations were unconfounded by sex, but limited the study as it was not possible to assess

whether the associations were different in women. Lastly, the study would have benefited from baseline information on blood lipids, although other studies have found lipids not to be an important confounder of the associations described and adjusting for treatment of high cholesterol (statin use) in the present study did not materially change the strength of the main association (Table S7)

Further research is required to investigate whether the strengths of the age-specific associations differ by stroke subtypes; whether there is effect modification of the associations for ischaemic heart disease and stroke subtypes by other vascular risk factors, such as smoking or alcohol intake; whether blood pressure is associated with less common vascular outcomes (such as atrial fibrillation, aortic aneurysm and heart failure); and also whether the findings are similar in women.

This study supports and strengthens the evidence that even at very old age there is a strong positive association between SBP and incidence of major vascular events. The present analyses did not include people with a history of vascular disease, to limit reverse causality, but clinical trials have found no evidence that the strength of association differs in those with and without a history of vascular disease. As those with a history of vascular disease are at high absolute risk of a major vascular events, the absolute effect of lowering blood pressure in this group is likely to be greater, on average, than those without such a history. These findings help to inform the decisions of clinicians and their patients when weighing the potential risks and benefits of hypertensive treatment. They also support public health initiatives which advocate lifestyle changes to address factors in this patient

406 group known to raise blood pressure, such as, obesity, physical inactivity, high
407 alcohol intake and high dietary salt intake.
408
409

Perspectives

In this prospective cohort study of older men, there was a positive association at age 65-94 years (mean age at event 80 years) between usual SBP and incidence of major vascular events throughout the blood pressure range examined (145-170 mmHg SBP). Each 10 mmHg higher usual SBP was associated with about 20% higher risk of major vascular events. There was evidence of a positive association with both ischaemic heart disease and stroke, and effect modification by age with shallower associations at older ages. Even at very old age (85-94 years), however, there was strong evidence of a positive association. Additional studies are warranted to determine the optimal timing and intensity for blood pressure-lowering interventions over the lifespan from middle to the oldest ages.

Acknowledgments

BL and GH conceived of the original idea for the paper. BL conducted the data analyses and produced the initial draft of the paper. BL, JG, BY, SL, KM, PN, LF, OA and GH were involved in the interpretation of the analyses and writing of the paper. BL, JG, BY, SL, KM, PN, LF, OA and GH approved the final version of the paper and take responsibility for its content. We thank the staff of the Data Linkage Unit, Health Department of Western Australia, Australia, for their excellent technical assistance, and the staff and management of Shenton Park Hospital for their support of the study. We especially thank all the men and staff who participated in the Western Australian Abdominal Aortic Aneurysm Program and the Health In Men Study.

Sources of Funding

BY is recipient of a Clinical Investigator Award from the Sylvia and Charles Viertel Charitable Foundation, New South Wales, Australia. JG is supported by grants from the National Health and Medical Research Council (1079369, 1079193, 1063476, 1022752, 1003707, 1021416, and 1000967), the Queensland Government and the Townsville Hospital Private Practice Trust. JG holds a Practitioner Fellowship from the National Health and Medical Research Council, Australia (1019921) and a Senior Clinical Research Fellowship from the Queensland Government. SL is funded by the UK Medical Research Council. The Health In Men Study is supported by grants from the National Health and Medical Research Council of Australia (964145, 139093, 403963, 455811, 1021416, 1000967, 1045710 and 1060557) with additional funding from the National Heart Foundation, the Western Australian Health Promotion Foundation (Healthway) and Fremantle Hospital Medical Research Foundation. The funding bodies played no role in generation of the data presented in this publication.

Conflicts of Interest Statement

None

References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2095-2128.
2. Prospective Studies Collaboration. 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;360:1903-1913.
3. Asia Pacific Cohort Studies Collaboration. Blood pressure and cardiovascular disease in the Asia Pacific region. *Journal of Hypertension*. 2003;21:707-716.
4. Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group. The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. *PloS One*. 2013;8:e65174.
5. Bejan-Angoulvant T, Saadatian-Elahi M, Wright JM, Schron EB, Lindholm LH, Fagard R, Staessen JA, Gueyffier F. Treatment of hypertension in patients 80 years and older: the lower the better? A meta-analysis of randomized controlled trials. *Journal of Hypertension*. 2010;28:1366-1372.
6. Blood Pressure Lowering Treatment Trialists Collaboration. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *BMJ*. 2008;336:1121-1123.
7. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009;338:b1665.
8. Norman PE, Flicker L, Almeida OP, Hankey GJ, Hyde Z, Jamrozik K. Cohort Profile: The Health In Men Study (HIMS). *International Journal of Epidemiology*. 2009;38:48-52.
9. Holman CD, Bass AJ, Rouse IL, Hobbs MS. Population-based linkage of health records in Western Australia: development of a health services

research linked database. *Australian and New Zealand Journal of Public Health*. 1999;23:453-459.

10. Clarke R, Shipley M, Lewington S, Youngman L, Collins R, Marmot M, Peto R. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol*. 1999;150:341-353.
11. Rosner B, Willett WC, Spiegelman D. Correction of logistic regression relative risk estimates and confidence intervals for systematic within-person measurement error. *Stat Med*. 1989;8:1051-69; discussion 1071-1073.
12. Fibrinogen Studies Collaboration. Regression dilution methods for meta-analysis: assessing long-term variability in plasma fibrinogen among 27,247 adults in 15 prospective studies. *Int J Epidemiol*. 2006;35:1570-1578.
13. Easton DF, Peto J, Babiker AG. Floating absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. *Statistics in Medicine*. 1991;10:1025-1035.
14. Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet*. 2009;373:1083-1096.
15. Asia Pacific Cohort Studies Collaboration. Blood pressure indices and cardiovascular disease in the Asia Pacific region: a pooled analysis. *Hypertension*. 2003;42:69-75.
16. Lawes CM, Bennett DA, Feigin VL, Rodgers A. Blood pressure and stroke: an overview of published reviews. *Stroke*. 2004;35:776-785.
17. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, White IR, Caulfield MJ, Deanfield JE, Smeeth L, Williams B, Hingorani A, Hemingway H. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *Lancet*. 2014;383:1899-1911.
18. HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *The New England Journal of Medicine*. 2008;358:1887-1898.
19. Barr EL, Tonkin AM, Welborn TA, Shaw JE. Validity of self-reported cardiovascular disease events in comparison to medical record adjudication and a statewide hospital morbidity database: the AusDiab study. *Intern Med J*. 2009;39:49-53.

20. Jamrozik E, Hyde Z, Alfonso H, Flicker L, Almeida O, Yeap B, Norman P, Hankey G and Jamrozik K. Validity of self-reported versus hospital-coded diagnosis of stroke: a cross-sectional and longitudinal study. *Cerebrovasc Dis*. 2014;37:256-262.

Novelty and Significance

1. What is New?

We conducted analyses that quantified the relation of systolic blood pressure (SBP) and incidence of major vascular events in older men (≥65 years). This study extends the findings of previous reports to show that even at very old age (85-94 years) there was strong evidence of a positive association.

2. What is Relevant?

The findings of this study add to the limited evidence on the relation between blood pressure and vascular disease at very old age.

3. Summary

Overall, 10 mmHg higher usual SBP was associated with about 20% higher risk of major vascular events (hazard ratio 19% [95%CI 13%-26%]; mean age at event 80 years). There was strong evidence of positive associations with ischaemic heart disease, stroke and other vascular disease. The associations were shallower at older ages, but even at age 85-94 years 10 mmHg higher usual SBP was associated with 14% (1%-30%) higher relative risk of major vascular events.

Figure Legends

Figure 1: Resurvey blood pressure versus baseline blood pressure (among 2862 resurveyed participants) β= slope of the regression line (equal to the regression dilution ratio).

Figure 2: Incidence of major vascular events versus usual SBP (among 7564 participants) Hazard ratios (adjusted for age at risk and education) at ages 65-94 years for major vascular events versus usual SBP were multiplied by a common factor (ie. floated) to make the weighted average match the annual incidence of major vascular events in this cohort. Annual incidence was the unweighted average of the component five-year incidence rates. For each category, area of square is inversely proportional to the variance of the category-specific log risk, which also determines the confidence interval. Incidence shown above each square and numbers of events below. Mean age at event was 80 years.

Table 1: Characteristics of the 7564 participants, by level of baseline SBP

Characteristics	Baseline SBP		
	<150 mmHg	150-169 mmHg	≥170 mmHg
Number of participants	2701	2764	2099
Mean (SD) age, years	71.2 (4.2)	71.6 (4.3)	72.2 (4.4)
No education beyond primary school, n (%)	568 (21.0)	593 (21.5)	454 (21.6)
Born in Australia, n (%)	1423 (52.7)	1566 (56.7)	1127 (53.7)
Current smokers, n (%)	305 (11.3)	298 (10.8)	237 (11.3)
Weekly drinkers, n (%)*	1691 (65.2)	1877 (71.0)	1391 (69.7)
Weekly vigorous exercise, n (%)	757 (28.0)	731 (26.4)	529 (25.2)
Mean (SD) BMI, kg/m^2	26.2 (3.6)	27.0 (3.6)	27.2 (3.8)
Self-reported diabetes, n (%)	232 (8.6)	280 (10.1)	229 (10.9)
Using cholesterol-lowering medication, n (%)*	235 (9.1)	299 (11.3)	206 (10.3)
Using blood pressure-lowering medication, n (%)*	462 (17.8)	761 (28.8)	763 (38.2)

*Information on alcohol intake and medication use was not collected in 332 men

Table 2: Incidence of major vascular events: hazard ratios per 10 mmHg higher usual SBP, by age at risk and type of vascular event (among 7564 participants)

Overall, and by age at risk and type of event	Number of events	Mean age at event, years	Hazard ratio (95% CI)
Overall	1557	79.8	1.19 (1.13-1.26)
Age at risk, years			
65-74	316	71.8	1.31 (1.15-1.48)
75-84	936	79.9	1.17 (1.09-1.26)
85-94	305	88.0	1.14 (1.01-1.30)
			Trend, 3 groups: χ^2_1=2.4 (p=0.12)
Type of event			
Ischaemic heart disease	833	79.4	1.19 (1.10-1.28)
Stroke	551	79.5	1.16 (1.05-1.27)
Other vascular	173	82.8	1.35 (1.14-1.59)
			Heterogeneity: χ^2_2 =2.5 (p=0.5)

Hazard ratios were adjusted for age at risk and education.

Table 3: Incidence of ischaemic heart disease and stroke: hazard ratios per 10 mmHg higher usual SBP, by age at risk (among 7564 participants)

Age at risk, years	Ischaemic heart disease			Stroke		
	Number of events	Mean age at event, years	Hazard ratio (95% CI)	Number of events	Mean age at event, years	Hazard ratio (95% CI)
65-74	200	71.8	1.28 (1.09-1.50)	103	71.8	1.43 (1.15-1.77)
75-84	472	79.7	1.21 (1.09-1.34)	362	79.8	1.12 (0.99-1.26)
85-94	161	88.0	1.04 (0.87-1.24)	86	87.5	1.02 (0.80-1.30)
			Trend, 3 groups: χ^2_1=2.8 (p=0.09)			Trend, 3 groups: χ^2_1=4.5 (p=0.03)
All	833	79.4	1.19 (1.10-1.28)	551	79.5	1.16 (1.05-1.27)

Hazard ratios are adjusted for age at risk and education.

Table 4: Comparison of different blood pressure indices (measured once only at baseline) as predictors of major vascular events: hazard ratios per 1-SD higher baseline levels of each blood pressure index (among 7564 participants)

Blood pressure index	Hazard ratio (95% CI) per 1-SD*			
	Ischaemic heart disease (833 events)	Stroke (551 events)	Other vascular (173 events)	All major vascular events (1557 events)
SBP	1.16 (1.09-1.24)	1.14 (1.05-1.23)	1.29 (1.12-1.49)	1.17 (1.11-1.23)
DBP	1.09 (1.02-1.17)	1.12 (1.03-1.22)	1.13 (0.97-1.31)	1.10 (1.05-1.16)
Mid blood pressure	1.15 (1.07-1.23)	1.14 (1.05-1.24)	1.26 (1.09-1.45)	1.16 (1.10-1.22)
Mean arterial pressure	1.14 (1.06-1.22)	1.14 (1.05-1.24)	1.23 (1.06-1.42)	1.15 (1.09-1.21)
Pulse pressure	1.14 (1.07-1.22)	1.09 (1.00-1.19)	1.28 (1.11-1.47)	1.14 (1.09-1.20)

Mid blood pressure = 1/2SBP+1/2DBP, mean arterial pressure = 1/3SBP+2/3DBP, pulse pressure = SBP-DBP.
* Hazard ratios are adjusted for age at risk and education, and uncorrected for regression dilution bias. SD of each blood pressure index: 20.7 mmHg for SBP, 11.4 mmHg for DBP, 14.7 mmHg for mid blood pressure, 13.2 mmHg for mean arterial pressure and 15.8 mmHg for pulse pressure.