Association between systolic blood pressure and dementia in the Whitehall II cohort study: role of age, duration, and threshold used to define hypertension

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Aims
To examine associations of diastolic and systolic blood pressure (SBP) at age 50, 60, and 70 years with incidence of dementia, and whether cardiovascular disease (CVD) over the follow-up mediates this association.

Methods and results
Systolic and diastolic blood pressure were measured on 8639 persons (32.5% women) from the Whitehall II cohort study in 1985, 1991, 1997, and 2003. Incidence of dementia (n_dementia/n_total = 385/8639) was ascertained from electronic health records followed-up until 2017. Cubic splines using continuous blood pressure measures suggested SBP >_130 mmHg at age 50 but not at age 60 or 70 was associated with increased risk of dementia, confirmed in Cox regression analyses adjusted for sociodemographic factors, health behaviours, and time varying chronic conditions [hazard ratio (HR) 1.38; 95% confidence interval (95% CI) 1.11, 1.70]. Diastolic blood pressure was not associated with dementia. Participants with longer exposure to hypertension (SBP >_ 130 mmHg) between mean ages of 45 and 61 years had an increased risk of dementia compared to those with no or low exposure to hypertension (HR 1.29, 95% CI 1.00, 1.66). In multi-state models, SBP > _ 130 mmHg at 50 years of age was associated with greater risk of dementia in those free of CVD over the follow-up (HR 1.47, 95% CI 1.15, 1.87).

Conclusion
Systolic blood pressure >_130 mmHg at age 50, below the conventional >_140 mmHg threshold used to define hypertension, is associated with increased risk of dementia; in these persons this excess risk is independent of CVD.

Keywords
Blood pressure • Dementia • Ageing
outstanding questions. One, ‘mid-life’ remains poorly characterized in studies, ranging from 35 to 68 years. Two, few studies have attempted to assess the impact of duration of hypertension using measures of blood pressure rather than reported use of antihypertensive medication. Three, it is unclear whether the 140 mmHg systolic blood pressure (SBP) threshold to define hypertension in mid-life is appropriate for dementia risk, given age-specific treatment targets recommended in recent reports aimed at reducing cardiovascular disease (CVD). To address some of these limitations, we examined the association between measured SBP and diastolic blood pressure (DBP) and dementia, focusing on the effects of age, duration of high blood pressure, and threshold of blood pressure to define hypertension in a large prospective cohort followed for 30 years. We hypothesize that hypertension in mid-life (at age 50) but not at older ages (age 70), is associated with risk of dementia. Given evidence of silent strokes and white matter lesions in those with hypertension, a second hypothesis we tested is that the association between hypertension at age 50 and incidence of dementia is only partially explained by clinical CVD over the follow-up.

Methods

The Whitehall II study is an ongoing study of 6895 men and 3413 women, aged 35–55 in 1985; follow-ups examinations were conducted in 1991 (n = 8815), 1997 (n = 7870), 2003 (n = 6967), 2007 (n = 6967), 2012 (n = 6318), and 2015 (n = 5632) with each wave taking 2 years to complete. Written informed consent from participants and research ethics approvals were renewed at each contact; the most recent approval was from the University College London Hospital Committee on the Ethics of Human Research, reference number 85/0938.

Blood pressure

Systolic and diastolic blood pressure were measured in the sitting position after 5 min of rest, using the Hawksley random-zero sphygmomanometer in 1985, 1991, and 1997 and an OMRON HEM 907 digital sphygmomanometer in 2003, 2007, and 2012. At each wave, two measures of SBP and DBP were taken and their mean was used in the analysis. Use of antihypertensive medication was self-reported at each contact.

Dementia

A comprehensive tracing of electronic health records, involving three databases, was used for dementia ascertainment: hospital episode statistics (HES) database, the Mental Health Services Data Set (MHSDS), and the mortality register using The International Classification of Disease, Tenth Revision (ICD-10) codes (F00–F04, G30, and G31), record linkage until 31 March 2017. These are national databases: HES and MHSDS contain information on both in- and out-patient care, with the latter also including data on care in the community. The validity of dementia cases in our study is supported by modelling changes in the global cognitive score in the 10 years before dementia diagnosis (Supplementary material online, figure S1) as in studies that use a ‘gold-standard’ dementia ascertainment procedure.

Covariates

Sociodemographic factors included age, sex, ethnicity (white, non-white), education, and occupational position. Health behaviours included smoking status (current, ex-, and never-smoker); alcohol consumption: non-drinkers, moderate alcohol consumption (1–14 units/week in women or 1–21 units/week in men), and heavy alcohol consumption (>14 units/week in women or >21 units/week in men), one unit of alcohol (UK) is defined as 10 ml (0.8 g) of pure alcohol; physical activity (h/week of moderate or vigorous physical activity, categorized as low <1 h, moderate between 1 and 2.5 h and high ≥2.5 h); and frequency of fruit and vegetable consumed per week (<once/day, once/day, or >once/day).

Health status. Body mass index (BMI, kg/m²) was calculated from measured height and weight. Diabetes was identified by fasting glucose ≥7.0 mmol/l, a 2-h post-load glucose ≥11.1 mmol/l, doctor-diagnosed diabetes, or use of diabetes medication. Coronary heart disease (CHD) by study specific assessments (12-lead resting electrocardiogram (ECG) recording, coded using the Minnesota system), self-reported CHD (verified in medical records), and linkage to HES (The International Classification of Disease, Ninth Revision (ICD-9) codes 410–414, ICD10 codes I20–I25, or procedures K40–K49, K50, K75, U19). Stroke using the MONICA–Augsburg stroke questionnaire, corroborated in HES (ICD9 430, 431, 434, 436 and ICD10 160–164). Atrial fibrillation assessment was based on data from a 12-lead resting ECG (Mingorec, Siemens Healthcare, Erlangen, Germany), Minnesota code 8.3 and data from HES (ICD9 code 427.3 and ICD10 code I48). Heart failure, based on HES records (ICD10 code I50). Use of medication for CVD was self-reported.

Statistical analysis

We extracted data on blood pressure at ages 50, 60, and 70 years for each participant across the data waves, allowing a ±5 year margin for each age category. The analysis of blood pressure at age 50, 60, and 70 years was based on 8639, 7558, and 4989 participants, respectively; the numbers differ due to non-response, death before age 60 or 70 or participants not having reached 70 years at the end of follow-up. We used inverse probability weighting (IPW) to ensure that analyses at ages 50, 60, and 70 reflected the same set of individuals. The probability of remaining in the study sample was estimated using data on sociodemographic, behavioural, cardiometabolic risk factors, chronic conditions, antihypertensive medication, and dementia status including its interaction with SBP and DBP and antihypertensive medication. The inverse of these probabilities were used to weight the data in Cox regression. The analyses, described below, were undertaken using STATA 14.1; the null hypothesis was rejected for two-sided values of P < 0.05.

Age and threshold of blood pressure and incidence of dementia

We used Cox regression with separate models for age 50, 60, and 70 years; the proportional hazard assumption was verified using Schoenfeld residuals. Date of entry was the date of clinical assessment from which the hypertension measure was drawn. Participants were censored at record of dementia, death, or 31 March 2017, whichever occurred first. We first examined the threshold of blood pressure at ages 50, 60, and 70 using restricted cubic spline regressions with Harrell knots; the command xbin20 was used to estimate adjusted HRs for the association of blood pressure (continuous measure in mmHg) with the risk of dementia. Once the threshold was identified, we used a dichotomous definition of hypertension to assess associations with dementia. The basic analysis was adjusted for sociodemographic (Model 1), then behavioural (Model 2), and finally also health-related factors (Model 3).

Duration of hypertension and incidence of dementia

Duration of hypertension status was estimated using data from 1985, 1991, 1997, and 2003 (mean age of participants 44.9 years in 1985 and 61.1 years in 2003) on 8313 participants who were alive and free of dementia in 2003 and had at least two assessments of hypertension status. Duration was summarized using group based trajectory modelling, fitted using the command traj in STATA. The association between hypertension trajectories (low,
incidence of dementia was associated with lower education, higher age at dementia diagnosis was 75.2 (standard deviation = 5.4) years.

Table 1

Characteristics at age 50 by dementia status at the end of follow-upa

| Characteristics at age 50 | Overall (n = 8639) | No dementia (n = 8254) | Dementia (n = 385) | P-valueb |
|--------------------------|-------------------|----------------------|-------------------|----------|
| Female, n (%)            | 2811 (32.5)       | 2642 (32.0)          | 169 (43.9)        | <0.001   |
| Non-white ethnicity, n (%) | 916 (10.6)       | 855 (10.4)           | 61 (15.8)         | <0.001   |
| No educational qualifications, n (%) | 913 (10.6) | 845 (10.2)           | 68 (17.7)         | <0.001   |
| Not married/cohabiting, n (%) | 2108 (24.4)     | 1996 (24.2)          | 112 (26.1)        | 0.028    |
| Low occupational position, n (%) | 1695 (19.6)     | 1551 (18.8)          | 144 (37.4)        | <0.001   |
| BMI, M (SD)              | 25.5 (3.8)        | 25.5 (3.8)           | 25.9 (4.0)        | 0.022    |
| Current smokers, n (%)  | 1345 (15.6)       | 1265 (15.3)          | 80 (20.8)         | 0.004    |
| Heavy alcohol consumptionc, n (%) | 1643 (19.0) | 1587 (19.2)          | 56 (14.6)         | <0.001   |
| Poor dietd, n (%)        | 3285 (38.0)       | 3117 (37.8)          | 168 (43.6)        | 0.003    |
| Low physical activity, n (%) | 2000 (23.2)      | 1884 (22.8)          | 116 (30.1)        | 0.003    |
| Diabetes, n (%)          | 193 (2.2)         | 180 (2.2)            | 13 (3.4)          | 0.121    |
| Systolic blood pressure, M (SD) | 122.1 (14.9)   | 121.9 (14.8)         | 126.3 (16.6)      | <0.001   |
| Diastolic blood pressure, M (SD) | 78.5 (10.3)   | 78.4 (10.3)          | 80.0 (10.8)       | 0.003    |
| Antihypertensive medication, n (%) | 492 (5.7)      | 467 (5.7)            | 25 (6.5)          | 0.49     |
| Cardiovascular disease, n (%) | 1654 (19.2)     | 1540 (18.7)          | 114 (29.6)        | <0.001   |
| Atrial fibrillation, n (%) | 758 (8.8)        | 698 (8.5)            | 60 (15.6)         | <0.001   |
| Heart failure, n (%)     | 262 (3.0)         | 236 (2.9)            | 26 (6.8)          | <0.001   |
| Cardiovascular medication, n (%) | 4564 (52.8)    | 4366 (52.9)          | 198 (51.4)        | 0.57     |

AF, atrial fibrillation; BMI, body mass index; CVD, cardiovascular disease; HF, heart failure; M, mean; SD, standard deviation.

aDementia status: start of follow-up at age 50 years, end of follow-up March 2017.
b2 tests (categorical data) and analysis of variance (continuous data).
cHeavy alcohol consumption was defined as >14 units/week in women and > 21 units/week in men.
dPoor diet was defined as fruit and vegetable consumption < once a day.
eParticipates who had experienced CVD, AF or HF from age 50 (baseline) to the end of the follow-up.
fParticipants who had ever reported taking cardiovascular medication over the follow-up.

Age and threshold of blood pressure and incidence of dementia

Continuous measures of blood pressure using cubic splines suggested increased risk of dementia with higher SBP starting from 130 mmHg at age 50 (Figure 1, Panel A). In contrast, no association was seen with SBP at age 60 (Figure 1, Panel B) or age 70 (Figure 1, Panel C). In order to ensure results were robust to overfitting we categorized SBP (<110, 110–119, 120–129, 130–139, >_140) and obtained similar results (Supplementary material online, Table S1). There was no association between DBP at age 50, 60, or 70 years and incidence of dementia (Supplementary material online, Figure S2).

In further analyses using Cox regression, SBP >_130 mmHg at age 50 was associated with increased hazard of dementia in the fully adjusted model [hazard ratio (HR) 1.38; 95% confidence interval (CI) 1.18, 1.60; Table 2]. No association was observed when SBP was measured at ages 60 or 70 years (Table 2). Further analysis using DBP threshold >90 mmHg in addition to SBP to define hypertension revealed similar results (Supplementary material online, Table S2).

Adding use of antihypertensive medication to SBP to define hypertension yielded results (Supplementary material online, Table S3) broadly similar to those presented in Table 2. In mutually adjusted models (data not tabulated), SBP >_130 mmHg at age 50 was associated with risk of dementia (HR 1.37; 95% CI 1.11, 1.70), while use of medication was not (HR 1.16, 95% CI 0.75, 1.80). However, at age 60, SBP

Results

Characteristics of 8639 participants at age 50 are presented in Table 1 as a function of dementia status over the follow-up. Mean age at dementia diagnosis was 75.2 (standard deviation = 5.4) years. Incidence of dementia was associated with lower education, higher blood pressure, and co-morbidities.
Sixteen-year hypertension trajectories (systolic blood pressure ≥130 mmHg) and incidence of dementia

Three hypertension trajectories were identified (model fit statistics in Supplementary material online, Table S4 and graphical representation in Supplementary material online, Figure S3): low, increasing, and high trajectories comprising 48.8%, 18.6%, and 32.7% of participants, respectively. Table 3 shows a higher hazard of dementia (Model 3, HR 1.29, 95% CI 1.00, 1.66) in the high trajectory group compared to those with low prevalence of hypertension with associations in the increasing trajectory group (Model 3, HR 1.15, 95% CI 0.84, 1.57) not statistically significant. In trajectories using SBP ≥130 mmHg and anti-hypertensive medication to define hypertension results were similar (Supplementary material online, Table S5).

Role of cardiovascular disease in the association between hypertension at age 50 and dementia

Figure 2 shows that in multi-state models, hypertension at age 50 was associated with a 1.34 times increased hazard of CVD (95% CI 1.22, 1.47). The association between hypertension at age 50 and dementia was not fully explained by CVD as demonstrated by the increased hazard of dementia in those free of CVD over the follow-up (HR 1.47, 95% CI 1.15, 1.87).

Discussion

The findings of this longitudinal observational study of over 8000 men and women support the hypothesis that hypertension in mid-life but not late life is associated with increased risk of dementia.3,5 We show that high SBP at age 50 was associated with increased risk of dementia, much under the conventional 140 mmHg threshold used to define hypertension. In our data, the excess risk was apparent at around 130 mmHg of SBP. Hypertension at age 70 was not associated with incidence of dementia. Longer exposure to hypertension in mid-life was associated with increased hazard of dementia. Although adjustment for CVD attenuated associations between hypertension at age 50 and dementia; multi-state models show this association to be present in those free of CVD, suggesting that clinical CVD does not fully account for the association between hypertension and dementia. These findings, highlighting the importance of elevated systolic pressure at age 50 as a risk factor for dementia need to be replicated in larger studies to allow elaboration of evidence based prevention.

The age-specific association between hypertension and dementia is widely acknowledged.3–5 Several prospective studies show high blood pressure in mid-life to be associated with increased risk of dementia,7,9,13 while the evidence of an association between hypertension in late life and dementia is less consistent.21–27 The age related variation in the association was shown within a single study in The Adult Changes in Thought Study, where high SBP was associated with dementia in the youngest age group but no association was found in older subjects.4 However, previous studies on mid-life hypertension cover a wide range of ages. In the Honolulu Asia Aging study, for example, mid-life was defined as ages between 45 and
### Table 2  Age and threshold of systolic blood pressure: association between hypertension and incidence of dementia^a^  

|                                      | n dementia / n total | Model 1 HR (95% CI) | Model 2 HR (95% CI) | Model 3 HR (95% CI) |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Hypertension at age 50 years (n = 8639) |                      |                      |                      |                      |
| Systolic blood pressure ≥140 mmHg    |                      |                      |                      |                      |
| No                                   | 311/7586             | 1.00                 | 1.00                 | 1.00                 |
| Yes                                  | 74/1053              | 1.39 (1.08, 1.80)    | 1.40 (1.09, 1.81)    | 1.30 (1.00, 1.69)    |
| Systolic blood pressure ≥130 mmHg    |                      |                      |                      |                      |
| No                                   | 228/6166             | 1.00                 | 1.00                 | 1.00                 |
| Yes                                  | 157/2473             | 1.45 (1.18, 1.79)    | 1.45 (1.18, 1.78)    | 1.38 (1.11, 1.70)    |
| Systolic blood pressure ≥120 mmHg    |                      |                      |                      |                      |
| No                                   | 147/4007             | 1.00                 | 1.00                 | 1.00                 |
| Yes                                  | 238/4632             | 1.20 (0.97, 1.48)    | 1.18 (0.96, 1.46)    | 1.10 (0.89, 1.37)    |
| Hypertension at age 60 years (n = 7558) |                      |                      |                      |                      |
| Systolic blood pressure ≥140 mmHg    |                      |                      |                      |                      |
| No                                   | 275/6219             | 1.00                 | 1.00                 | 1.00                 |
| Yes                                  | 65/1339              | 1.16 (0.87, 1.54)    | 1.15 (0.87, 1.53)    | 1.15 (0.87, 1.53)    |
| Systolic blood pressure ≥130 mmHg    |                      |                      |                      |                      |
| No                                   | 211/4811             | 1.00                 | 1.00                 | 1.00                 |
| Yes                                  | 129/2747             | 1.05 (0.84, 1.32)    | 1.06 (0.84, 1.33)    | 1.03 (0.82, 1.31)    |
| Systolic blood pressure ≥120 mmHg    |                      |                      |                      |                      |
| No                                   | 131/2936             | 1.00                 | 1.00                 | 1.00                 |
| Yes                                  | 209/4622             | 1.07 (0.85, 1.34)    | 1.08 (0.86, 1.36)    | 1.06 (0.84, 1.34)    |
| Hypertension at age 70 years (n = 4989) |                      |                      |                      |                      |
| Systolic blood pressure ≥140 mmHg    |                      |                      |                      |                      |
| No                                   | 176/3722             | 1.00                 | 1.00                 | 1.00                 |
| Yes                                  | 69/1267              | 1.00 (0.73, 1.36)    | 0.98 (0.71, 1.34)    | 1.03 (0.74, 1.43)    |
| Systolic blood pressure ≥130 mmHg    |                      |                      |                      |                      |
| No                                   | 121/2694             | 1.00                 | 1.00                 | 1.00                 |
| Yes                                  | 124/2295             | 1.07 (0.80, 1.42)    | 1.06 (0.80, 1.42)    | 1.14 (0.85, 1.54)    |
| Systolic blood pressure ≥120 mmHg    |                      |                      |                      |                      |
| No                                   | 69/1463              | 1.00                 | 1.00                 | 1.00                 |
| Yes                                  | 176/3526             | 1.07 (0.78, 1.46)    | 1.06 (0.78, 1.45)    | 1.19 (0.86, 1.64)    |

Model 1: Adjusted for age, sex, education, ethnicity, marital status, and occupational position.
Model 2: Model 1 + health behaviours.
Model 3: Model 2 + BMI, diabetes at start of follow-up + time-dependent cardiovascular disease (coronary heart disease, stroke), atrial fibrillation, heart failure, and cardiovascular medication.
CI, confidence interval; HR, hazard ratio.
^a^Analysis using inverse probability weighting in Cox regression.

### Table 3  Duration of hypertension (systolic blood pressure ≥130 mmHg) trajectories^a^ with incidence of dementia^b^  

|                                      | n cases/n total | Model 1 HR (95% CI) | Model 2 HR (95% CI) | Model 3 HR (95% CI) |
|--------------------------------------|-----------------|----------------------|----------------------|----------------------|
| Hypertension trajectories (data from 1985, 1991, 1997, 2003) |                 |                      |                      |                      |
| Group 1: Low                         | 135/4054        | 1.00                 | 1.00                 | 1.00                 |
| Group 2: Increasing                  | 65/1545         | 1.08 (0.80, 1.47)    | 1.12 (0.82, 1.53)    | 1.15 (0.84, 1.57)    |
| Group 3: High                        | 158/2714        | 1.30 (1.02, 1.65)    | 1.31 (1.02, 1.68)    | 1.29 (1.00, 1.66)    |

Model 1: Adjusted for age, sex, education, ethnicity, marital status, and occupational position.
Model 2: Model 1 + health behaviours.
Model 3: Model 2 + BMI, diabetes at start of follow-up + time-dependent cardiovascular disease (coronary heart disease, stroke), atrial fibrillation, heart failure, and cardiovascular medication.
CI, confidence interval; HR, hazard ratio.
^a^Trajectories over a mean 16 year period; further information in Supplementary material online, Figure S3 and Table S4.
^b^Analysis using inverse probability weighting in Cox regression.
68 years, an age-range greater than two decades. Poor characterization of the age when hypertension carries a risk is also reflected in dementia guidelines as they only use the generic term ‘mid-life’. Our data show considerable differences in dementia risk over the two decade age-span, elevated SBP at age 50 but not at age 60 increased risk of dementia.

One of the key reasons proposed for the importance of mid-life hypertension on brain health is due to duration of exposure, as those with hypertension at age 50 are likely to be ‘exposed’ for longer. Direct assessment of duration of hypertensive status over many years is rare; many studies use a single measure of hypertension. An exception is the AGES study which used two measures of hypertension to examine the interaction between mid-life hypertension and late-life hypertension, separated by 26 years. They found that mid-life hypertension modifies the relationship between late-life blood pressure and cognitive performance. However, this study had no information on hypertension status between these two assessments and therefore the protective effects of later life hypertension may reflect a shorter duration of hypertension.

Hypertension is currently classified by SBP or DBP >140/90 mmHg although in the majority of studies in this area a higher threshold (160/95 mmHg) has been used to define hypertension. However, age-specific treatment targets are being suggested for the reduction of CVD risk with a recent recommendation of SBP < 120 mmHg for those 50 years and younger. Trial data on the benefits of reducing SBP on cognitive outcomes is not conclusive; however, all the research in this domain is based on older adults and whether better control of blood pressure at younger ages modifies risk for dementia is unknown.

Hypertension is known to be associated with silent strokes, white matter lesions, and impairment of cerebral circulation leading to ischaemic injury. This suggests that part of the association of hypertension with dementia may not be explained by clinical CVD, a hypothesis that we were able to test using multi-state models which allow incorporation of both incident CVD and dementia over the follow-up. Our results show excess risk of dementia is also present in those free of CVD. These results suggest that subclinical or ‘silent’ vascular brain lesions (i.e. infarcts, microbleeds, white matter changes), which are common in those with hypertension may be involved in increased dementia risk in those with high blood pressure who do not have clinical CVD. Thus, cerebral small vessel disease is likely to be an important mechanism underlying the association of high blood pressure and cognitive dysfunction.

A limitation of the study is use of linkage to electronic health records for dementia ascertainment, a method that has high specificity but is likely to miss milder cases of dementia. There was no evidence in our data that hypertension affected age of dementia diagnosis, it was 75.3 and 75.2 years in groups defined by SBP > 130 mmHg (yes/no) at age 50 (P = 0.85). Thus, any misclassification of dementia status is likely to be random, i.e. the probability of dementia status being misclassified is independent of hypertension at age 50. Under conditions of high specificity, the association between risk factor and outcome is unlikely to be biased by under-ascertainment of the outcome. Furthermore, under-ascertainment of dementia is unlikely to lead to the age-specific patterns observed in our study. Another limitation is that we were not able to examine whether the association of hypertension was stronger with Alzheimer’s or vascular dementia due to small numbers. Random measurement error in the blood pressure readings may have diluted associations but it is unlikely to lead to the pattern of results observed for SBP at 50, 60, and 70 years. Finally, residual confounding cannot be ruled out in observational studies but it is unlikely that bias would lead to the pattern of results observed in our study.

Strengths of the study are linked to the availability of repeat data on blood pressure and a long follow-up for dementia. Thus, both ‘timing’ and ‘duration’ which seem to be key to understanding the role of hypertension in dementia, could be examined. However, some misclassification is possible as blood pressure was assessed only every 4 years, and we did not have data on ambulatory blood pressure. A further strength is use of measured blood pressure rather than self-reported antihypertensive use to define hypertension, ensuring that reporting or non-compliance which can be considerable in observational studies do not bias our results. This approach also allows the development of clear neuroprotective guidelines, contributing to the debate on the correct target for blood pressure. Finally, the use of IPW ensures that missing data do not affect results, as they are known to be more common in those at greater risk of adverse health outcomes.

**Conclusion**

Hypertension is a known risk factor for CVD, renal failure, and premature mortality. It is also highly prevalent; number of persons with elevated SBP continues to increase globally and may affect dementia risk either directly or via processes related to CVD. Our study highlights the detrimental effects of mid-life hypertension, here at age 50 years, and increase in risk at levels below that used to treat SBP.
**Supplementary material**

**Supplementary material** is available at European Heart Journal online.

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**Conflict of interest**

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