**Associations of blood pressure trajectories with subsequent cognitive decline, dementia and mortality**

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Supplemental Figure 8. Subgroup analyses on antihypertensive medication use for association between each SD increment in trajectories of diastolic blood pressure and global cognitive decline (SD/year), risk of incident dementia and all-cause mortality

**Supplemental methods**

1. Description of the covariates

Covariates were adjusted using either time-varying or time-fixed fashion. For time-fixed fashion, we adjusted demographic and clinical characteristics assessed at wave 1. Demographics included age (years), sex, ethnicity (of white ethnicity or not), educational background (high-level education or not), cohabitation status (living alone or not). Clinical characteristics included body mass index (BMI, kg/m2), diabetes, hyperlipidemia, stroke, personal history of heart diseases (including heart attack, coronary heart disease, angina, congestive heart failure, and any other heart diseases), cancer, and chronic lung disease. Among them, cancer, and chronic lung disease were only served as covariates for mortality outcome due to their specific relevance to mortality risk.

For time-varying fashion, we used the total number of waves reporting the following conditions, including current smoking (yes or no), alcohol consumption (at least once per week), physical activity (engaging in vigorous or moderate activities no less than once weekly), depressive symptoms (yes or no) and antihypertensive medication use. Period for defining time-varying covariates was waves 1 to 4. The original binary values (0 and 1) were expanded to a range of 0 to 4 for these time-varying variables. For instance, a value of 3 for current smoking indicates that smoking was reported in 3 out of 4 waves, while a value of 0 signifies non-smoking reported in all 4 waves. High-level education was defined as above senior level of high school or 12 or more years of education. Depressive symptoms were evaluated based on an 8-item version of the Center for Epidemiologic Studies Depression Scale (CESD-8, one point for each item), with scores ≥ 4 were regarded as having depressive symptoms. Personal history of stroke, heart diseases, cancer, and chronic lung disease was derived from records of self-reported physician-diagnosed diseases. Hypertension was defined as physician-confirmed diagnosis or mean SBP/DBP ≥140/90 mm Hg or used antihypertensive medications. Diabetes was defined as physician-confirmed diagnosis or fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L) or an HbA1c level ≥48 mmol/mol (6.5%) or insulin injection. Hyperlipidemia was defined as total cholesterol level ≥ 240 mg/dL (6.216 mmol/L) or regular use of lipid-lowering medications.

1. Trajectory modelling methods

Group-based trajectory modeling enabled us to simultaneously estimate the probabilities for multiple trajectories as opposed to simply fitting the overall population mean. Then the grouping was achieved by estimating the posterior probabilities of each participant belonging to each potential trajectory group and those with the highest probability was determined as the final group membership. We used model fit statistics to evaluate model fitting and tested models with different number and shape of trajectories. To determine the best-fit number and shape of trajectories, we estimated separate trajectory models with the number of groups set from 2 to 6, and tested linear, quadratic, and cubic terms to determine the shape that best represents the trajectories. A censored normal model form was used. After comparing model fit statistics of the Bayesian information criterion (BIC) of different trajectory models, the five-trajectory group model was selected as the best model for both trajectories of systolic and diastolic blood pressures, and was used in subsequent analyses.

**Table S1.** **Comparison of baseline characteristics between participants and those excluded in the ELSA study**

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | Included  (n=7566) | Excluded  (n=11904) | *P value* |
| Age, year | 62.0 [55.0, 70.0] | 65.0 [55.0, 75.0] | <0.001 |
| Male sex, n (%) | 3387 (44.8) | 4861 (40.8) | <0.001 |
| White race, n (%) | 7435 (98.3) | 9983 (83.9) | <0.001 |
| High-level education, n (%) | 963 (12.7) | 1274 (10.7) | <0.001 |
| Living alone, n (%) | 2473 (32.7) | 1618 (13.6) | <0.001 |
| Current smoking, n (%) | 1261 (16.7) | 901 (7.6) | <0.001 |
| Alcohol consumption, n (%) | 5356 (70.8) | 2510 (21.1) | <0.001 |
| Physical activity, n (%) | 6027 (79.7) | 2882 (24.2) | <0.001 |
| Depressive symptoms (CES-D≥12), n (%) | 1078 (14.2) | 863 (7.2) | <0.001 |
| BMI, mean(SD)，kg/m2 | 27.0±5.6 | 16.8±13.5 | <0.001 |
| SBP, mean(SD)，mmHg | 141.3±19.5 | 144.9±26.2 | <0.001 |
| DBP, mean(SD)，mmHg | 78.0±12.2 | 78.9±19.8 | 0.015 |
| Hypertension, n (%) | 4212 (55.7) | 2484 (20.9) | <0.001 |
| Diabetes, n (%) | 635 (8.4) | 410 (3.4) | <0.001 |
| Hyperlipidemia, n (%) | 4263 (56.3) | 8491 (71.3) | <0.001 |
| Stroke, n (%) | 250 (3.3) | 265 (2.2) | <0.001 |
| Heart diseases, n (%) | 1104 (14.6) | 934 (7.8) | <0.001 |
| Chronic lung disease, n (%) | 423 (5.6) | 340 (2.9) | <0.001 |
| Cancer, n (%) | 439 (5.8) | 288 (2.4) | <0.001 |
| Memory score | 9.9±3.4 | 6.7±5.5 | <0.001 |
| Verbal Fluency score | 20.1±6.2 | 13.6±10.7 | <0.001 |
| Temporal orientation score | 4.0 [4.0, 4.0] | 4.0 [3.0, 4.0] | <0.001 |

a Values are mean (standard deviation) or median (quartile 1–quartile 3) for continuous variables and number (%) for categorical variables.

b P value reported for differences between two populations using t test, chi-square test, or Wilcoxon rank test.

**Table S2. Memory impact of trajectories of blood pressures**

|  |  |  |
| --- | --- | --- |
| Trajectories of blood pressure | Decline rate (SD/year) | |
| β (95% CI) a | *P* value |
| **Trajectories of systolic blood pressure** |  |  |
| Normal-stable | Reference |  |
| Normal-high stable | -0.014 (-0.021, -0.006) | <0.001 |
| Moderate-stable | -0.016 (-0.028, -0.005) | 0.007 |
| High-falling | -0.026 (-0.048, -0.004) | 0.022 |
| High-stable | -0.049 (-0.091, -0.007) | 0.023 |
| **Trajectories of diastolic blood pressure** |  |  |
| Normal-stable | Reference |  |
| Low-stable | -0.010 (-0.025, 0.006) | 0.218 |
| Moderate-low stable | -0.012 (-0.019, -0.005) | 0.001 |
| Moderate-high stable | -0.015 (-0.032, 0.001) | 0.072 |
| Moderate-decreasing | -0.007 (-0.037, 0.022) | 0.629 |

a Adjusted covariates included age, sex, ethnicity, education, cohabitation status, body mass index, diabetes, stroke, cardiovascular diseases, hyperlipidemia as well as total number of waves reporting current smoking, alcohol consumption, physical activity, depressive symptoms, and antihypertensive medication usage.

**Table S3. Verbal Fluency impact of trajectories of blood pressures**

|  |  |  |
| --- | --- | --- |
| Trajectories of blood pressure | Decline rate (SD/year) | |
| β (95% CI) a | *P* value |
| **Trajectories of systolic blood pressure** |  |  |
| Normal-stable | Reference |  |
| Normal-high stable | -0.010 (-0.018, -0.002) | 0.019 |
| Moderate-stable | -0.014 (-0.026, -0.002) | 0.026 |
| High-falling | -0.011 (-0.035, 0.012) | 0.347 |
| High-stable | -0.022 (-0.067, 0.022) | 0.325 |
| **Trajectories of diastolic blood pressure** |  |  |
| Normal-stable | Reference |  |
| Low-stable | -0.008 (-0.024, 0.009) | 0.351 |
| Moderate-low stable | -0.007 (-0.015, 0.000) | 0.053 |
| Moderate-high stable | -0.004 (-0.021, 0.014) | 0.673 |
| Moderate-decreasing | 0.008 (-0.023, 0.038) | 0.632 |

a Adjusted covariates included age, sex, ethnicity, education, cohabitation status, body mass index, diabetes, stroke, cardiovascular diseases, hyperlipidemia as well as total number of waves reporting current smoking, alcohol consumption, physical activity, depressive symptoms, and antihypertensive medication usage.

**Table S4. Temporal orientation impact of trajectories of blood pressures**

|  |  |  |
| --- | --- | --- |
| Trajectories of blood pressure | Decline rate (SD/year) | |
| β (95% CI) a | *P* value |
| **Trajectories of systolic blood pressure** |  |  |
| Normal-stable | Reference |  |
| Normal-high stable | -0.008 (-0.018, 0.001) | 0.092 |
| Moderate-stable | -0.010 (-0.024, 0.005) | 0.194 |
| High-falling | -0.029 (-0.057, -0.002) | 0.037 |
| High-stable | -0.046 (-0.098, 0.006) | 0.083 |
| **Trajectories of diastolic blood pressure** |  |  |
| Normal-stable | Reference |  |
| Low-stable | -0.022 (-0.041, -0.003) | 0.025 |
| Moderate-low stable | -0.018 (-0.027, -0.010) | <0.001 |
| Moderate-high stable | -0.010 (-0.031, 0.010) | 0.318 |
| Moderate-decreasing | -0.013 (-0.050, 0.024) | 0.494 |

a Adjusted covariates included age, sex, ethnicity, education, cohabitation status, body mass index, diabetes, stroke, cardiovascular diseases, hyperlipidemia as well as total number of waves reporting current smoking, alcohol consumption, physical activity, depressive symptoms, and antihypertensive medication usage.

**Table S5. Associations of blood pressure trajectories with subsequent cognitive global Z scores for memory and verbal fluency only**

|  |  |  |
| --- | --- | --- |
| Trajectories of blood pressure | Global cognitive decline rate (SD/year) | |
| β (95% CI) a | *P* value |
| **Trajectories of systolic blood pressure** |  |  |
| Normal stable | Reference |  |
| Normal-high stable | -0.015 (-0.023, -0.007) | <0.001 |
| Moderate-stable | -0.020 (-0.033, -0.008) | 0.002 |
| High-falling | -0.025 (-0.049, -0.001) | 0.040 |
| High-stable | -0.050 (-0.095, -0.004) | 0.032 |
| **Trajectories of diastolic blood pressure** |  |  |
| Normal stable | Reference |  |
| Low-stable | -0.014 (-0.038, -0.003) | 0.109 |
| Moderate-low stable | -0.013 (-0.027, -0.011) | <0.001 |
| Moderate-high stable | -0.013 (-0.038, -0.001) | 0.151 |
| Moderate-decreasing | 0.001 (-0.039, 0.028) | 0.946 |

a Adjusted covariates included age, sex, ethnicity, education, cohabitation status, body mass index, diabetes, stroke, cardiovascular diseases, hyperlipidemia as well as total number of waves reporting current smoking, alcohol consumption, physical activity, depressive symptoms, and antihypertensive medication usage.

**Table S6. Associations of blood pressure trajectories with subsequent risk of dementia, results from competing risk regression models**

|  |  |  |  |
| --- | --- | --- | --- |
| Trajectories of blood pressure | Incident dementia | | |
| Event/N | HR (95%CI) a | P value |
| **Trajectories of systolic blood pressure** |  |  |  |
| Normal-stable | 142/2008 | Reference |  |
| Normal-high stable | 444/4180 | 1.40 (1.15, 1.70) | <0.001 |
| Moderate-stable | 136/1038 | 1.78 (1.39, 2.28) | <0.001 |
| High-falling | 32/255 | 1.47 (0.97, 2.22) | 0.072 |
| High-stable | 17/85 | 2.79 (1.65, 4.72) | <0.001 |
| **Trajectories of diastolic blood pressure** |  |  |  |
| Normal-stable | 254/3032 | Reference |  |
| Low-stable | 54/514 | 1.16 (0.84, 1.60) | 0.375 |
| Moderate-low stable | 415/3545 | 1.39 (1.18, 1.64) | <0.001 |
| Moderate-high stable | 35/368 | 1.04 (0.73, 1.49) | 0.822 |
| Moderate-decreasing | 13/107 | 1.18 (0.66, 2.12) | 0.568 |

a Adjusted covariates included sex, age × time, ethnicity, education, cohabitation status, body mass index, diabetes, stroke, cardiovascular diseases, hyperlipidemia as well as total number of waves reporting current smoking, alcohol consumption, physical activity, depressive symptoms, and antihypertensive medication usage.

**Table S7. Associations of blood pressure trajectories with subsequent risk of dementia using a stricter definition a**

|  |  |  |  |
| --- | --- | --- | --- |
| Trajectories of blood pressure | Incident dementia | | |
| Event/N | HR (95%CI) b | P value |
| **Trajectories of systolic blood pressure** |  |  |  |
| Normal-stable | 115/2008 | Reference |  |
| Normal-high stable | 345/4180 | 1.40 (1.15, 1.70) | <0.001 |
| Moderate-stable | 109/1038 | 1.78 (1.39, 2.28) | <0.001 |
| High-falling | 26/255 | 1.47 (0.97, 2.22) | 0.072 |
| High-stable | 8/85 | 2.79 (1.65, 4.72) | <0.001 |
| **Trajectories of diastolic blood pressure** |  |  |  |
| Normal-stable | 190/3032 | Reference |  |
| Low-stable | 46/514 | 1.16 (0.84, 1.60) | 0.375 |
| Moderate-low stable | 330/3545 | 1.39 (1.18, 1.64) | <0.001 |
| Moderate-high stable | 26/368 | 1.04 (0.73, 1.49) | 0.822 |
| Moderate-decreasing | 11/107 | 1.18 (0.66, 2.12) | 0.568 |

1. The stricter definition of dementia was defined by either self-reported physician diagnosis or an alternative approach based on the concurrent cognitive and functional impairment, which needed to persist for at least two consecutive waves.
2. Adjusted covariates included sex, age × time, ethnicity, education, cohabitation status, body mass index, diabetes, stroke, cardiovascular diseases, hyperlipidemia as well as total number of waves reporting current smoking, alcohol consumption, physical activity, depressive symptoms, and antihypertensive medication usage.

**Figure S1. Timeline and procedures of the study.**

**Figure S2. Flow chart showing process of inclusion of the study population**



**Figure S3. Subgroup analyses on age for association between each SD increment in trajectories of systolic blood pressure and global cognitive decline (SD/year), risk of incident dementia and all-cause mortality**

**Figure S4. Subgroup analyses on sex for association between each SD increment in trajectories of systolic blood pressure and global cognitive decline (SD/year), risk of incident dementia and all-cause mortality**

**Figure S5. Subgroup analyses on antihypertensive medication use for association between each SD increment in trajectories of systolic blood pressure and global cognitive decline (SD/year), risk of incident dementia and all-cause mortality**

**Figure S6. Subgroup analyses on age for association between each SD increment in trajectories of diastolic blood pressure and global cognitive decline (SD/year), risk of incident dementia and all-cause mortality**

**Figure S7. Subgroup analyses on sex for association between each SD increment in trajectories of diastolic blood pressure and global cognitive decline (SD/year), risk of incident dementia and all-cause mortality**



**Figure S8. Subgroup analyses on antihypertensive medication use for association between each SD increment in trajectories of diastolic blood pressure and global cognitive decline (SD/year), risk of incident dementia and all-cause mortality**