

Orthostatic Hypotension and Risk of Incident Dementia Results From a 12-Year Follow-Up of the Three-City Study Cohort

Antoine Cremer, Aïcha Soumaré, Claudine Berr, Jean-François Dartigues, Audrey Gabelle,
Philippe Gosse, Christophe Tzourio

Abstract—Several studies indicate a potential link between orthostatic hypotension (OH) and incident dementia but without substantial evidence to date. Our objective is to study the association between OH and dementia in a cohort of elderly individuals. To do so, baseline lying and standing blood pressure measurements were taken from 7425 subjects in the Three-City study. These subjects were then followed-up for 12 years. Cox proportional hazard models, adjusted for potential confounders, were used to estimate the risk of incident dementia according to OH status. Sensitivity analysis was performed using the so-called illness-death model, a specific statistical method which takes into account competitive risk with death. OH frequency was found to be around 13%, and 760 cases of dementia were diagnosed during follow-up. We observed significant associations between the presence of OH at baseline and the occurrence of dementia during the follow-up, with an increased risk of at least 25% observed regardless of the OH threshold and the statistical method used. In conclusion, there is an association between OH and dementia. Considering that OH is a common condition and is easy to measure, OH measurements could help to identify subjects with higher risk of dementia. Moreover, reducing OH could be a step to prevent conversion to dementia. (*Hypertension*. 2017;70:44-49. DOI: 10.1161/HYPERTENSIONAHA.117.09048.) • [Online Data Supplement](#)

Key Words: blood pressure ■ dementia ■ orthostatic hypotension ■ risk ■ vascular ageing community-based cohort

In clinical practice, orthostatic hypotension (OH), a blood pressure drop in standing position, is a common condition affecting at least 6% of the population.¹ OH has been consistently associated with increased mortality and risk of cardiovascular events.² This leads us to question whether cerebral perfusion variations induced by OH could contribute to an increased risk of dementia. An increase in the prevalence of OH in patients with dementia,³ as well as increased risk of conversion to dementia, has been shown among patients with mild cognitive impairment and OH.⁴ In general population, relationships between OH and cognitive impairments are highlighted⁵⁻⁸ but without drawing substantive conclusions given the too short duration of the follow-up and insufficient number of subjects or as a result of an unequal distribution of the Mini-Mental State Examination score according to OH status. Given these results, there is currently no significant evidence to support the prospective relationship between OH and the risk of dementia.

The Three-City study, a community-based cohort of 9294 individuals above the age of 65 years with a follow-up of 12 years,⁹ thus, seems to be an adequate resource to attempt to make progress on this research topic.

Methods

Study Population

The principal objective of the Three-City study was to examine the vascular determining factors of incident dementia.⁹ The study participants, aged ≥65 years, noninstitutionalized, were recruited from 1999 to 2001 (inclusive) on a voluntary basis using the electoral rolls in 3 French cities: Bordeaux, Dijon, and Montpellier. There was a 37% acceptance rate among the contacted subjects. After excluding those who refused to participate in the medical interview (n=392), the sample comprised 9294 participants (Bordeaux, n=2104; Montpellier, n=2259; and Dijon, n=4931). The initial interview took place either in a health center or at the subject's home and consisted of a face-to-face interview with a trained investigator to collect data related to background information, life-style, and medical history. In addition, a fasting blood sample was taken, and physical and cognitive assessments were performed. During the 12-year follow-up period, 5 follow-up visits took place every 2 or 3 years.

The working sample of this study consisted of subjects without prevalent dementia and who had their blood pressure measured while sitting and standing at baseline.

Diagnosis of Dementia

Diagnosis of dementia was based on a 3-step procedure at each follow-up screening, as described elsewhere.¹⁰

Received January 9, 2017; first decision January 23, 2017; revision accepted April 28, 2017.

From the Department of Cardiology and Hypertension, Bordeaux University Hospital, France (A.C., P.G.); University of Bordeaux, Inserm, Bordeaux Population Health Research Center, France (A.C., A.S., J.-F.D., C.T.); CHU de Bordeaux, Pole de sante publique, Service d'information medicale, F-33000 Bordeaux, France (A.C., A.S., J.-F.D., C.T.); INSERM Unité 1061, Neuropsychiatrie: Recherche Epidemiologique et Clinique, Montpellier, France (C.B.); and Department of Neurology, Montpellier University Hospital, France (A.G.)

The online-only Data Supplement is available with this article at <http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.117.09048/-DC1>.

Correspondence to Antoine Cremer, Unité de cardiologie et d'hypertension artérielle, Hôpital Saint André, CHU de Bordeaux, 1 rue Jean Burguet 33000 Bordeaux, France. E-mail antoine.cremer@chu-bordeaux.fr

© 2017 American Heart Association, Inc.

Hypertension is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.117.09048

First, at baseline and at each follow-up visit, trained psychologists assessed cognitive function, and dementia was actively screened. Depending on the score obtained in the Mini-Mental State Examination and Isaac test, subjects could be identified as at risk for dementia.¹¹ On the Bordeaux and Montpellier sites, a neurologist evaluated all subjects. However, and because of a large number of subjects, only at-risk subjects were evaluated by the neurologist on the Dijon site. Finally, after this examination based on clinical evaluation, the final diagnosis of dementia was made by an independent panel of neurologists and geriatricians with a strong expertise in dementia. They used the information available from the Three-City study examination and all exams performed by the patients' physicians who could include, but not systematically, neuroimaging exams. The diagnosis of dementia was established on the basis of the Diagnosis and Statistical Manual of Mental Disorders-IV from the American Psychiatric Association. Alzheimer's disease was classified as possible or probable, using the criteria of the National Institute of Neurological and Communication Disorders and Stroke and of the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA criteria).¹²

Blood Pressure Measurement and Diagnosis of OH

The protocol for blood pressure measurement has been described previously.⁹

For OH diagnosis, participants had to first lie down and relax for at least 5 minutes. Then, an appropriate size cuff was placed on the right arm, close to the level of the heart. The measuring devices used consisted of automatic oscillometric devices developed by OMRON CP750 (Japan) rated A/A by the British Hypertension Society.¹³ Blood pressure was measured once in lying position. After this measurement in lying position and without removing the cuff, the participant had to stand up, and then another one blood pressure measurement was immediately performed in standing position without delay. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) values and heart rate were also recorded in the database. No data on symptoms that could potentially indicate a drop in BP were recorded. Standing blood pressures were not measured during the follow-up.

The diagnosis of OH is based on a consensus, and there are several diagnostic thresholds defined in the literature. We conducted analysis not only with the most consensual threshold (a reduction in SBP of at least 20 mm Hg or DBP of at least 10 mm Hg¹⁴) but also with 2 other thresholds commonly referred to as mild OH (reduction in SBP of at least 10 mm Hg or DBP of at least 5 mm Hg)¹⁵ and severe OH (reduction in SBP of at least 30 mm Hg or DBP of at least 15 mm Hg).¹⁶

For hypertension diagnosis, 2 series of blood pressure measurements were conducted, the first at the beginning of the interview and the second after the ECG to diagnose OH for the Bordeaux and Dijon centers. In Montpellier, only 1 series of blood pressure measurements was performed after the ECG, which was, therefore, the same measurement used to diagnose OH and hypertension.

Hypertension was defined as an SBP \geq 140 mm Hg, a DBP \geq 90 mm Hg, or taking antihypertensive drugs.

Clinical Events and Death During Follow-Up

During follow-up, participants were asked to declare their cardiovascular history (interview or questionnaire). This included information on previous coronary events (acute coronary syndrome, myocardial revascularization) and stroke, regardless of the cause. If the subject answered affirmatively, the potential cases were further documented by medical data obtained from general practitioners, specialists, and hospital records where possible and were reviewed by 2 panels of experts, 1 for coronary events and 1 for stroke.

Mortality was ascertained from the civil registry by systematic request for all subjects not included in follow-up visits. The date of death was defined as the date of event and the date of the last follow-up or phone contact for the 10-year follow-up as the date of censoring.

Other Variables

The level of education was divided into 4 categories from no school or only primary schooling to participants with studies in higher education.

The Mini-Mental State Examination score was used to determine cognitive state. If the score was \geq 24/30, we considered the subject's cognitive state as normal.¹⁷ Scores below this threshold were used to define a cognitive impairment.

Diabetic status was defined by a level of fasting blood glucose >7 mmol/L or the intake of antidiabetic treatment (oral treatment or insulin).

Smoking status accounted for nonsmokers and former and active smokers. Former smokers were defined as having had quit smoking for at least 6 months.

Subjects were considered dyslipidemic if their total cholesterol level was >5.2 mmol/L or if they were under hypolipidemic treatment.

Hypotensive medication was defined by the taking of medication which decreases the blood pressure whatever the indication: hypertension or other cardiovascular condition.

Psychotropic medication was defined by the taking of a chronic treatment for psychiatric disorder.

The diagnosis of depression was established on the basis of the score obtained on the depression scale established by the Center for Epidemiology Studies-Depression. Depression in a subject was defined by a score of >16 for men and >23 for women.¹⁸

Statistical Analysis

Participants who did not have their blood pressure measured in standing position were removed from the analysis but were compared with the cohort whose blood pressure was measured while standing to determine whether these values were missing at random. Comparative statistical tests adapted to independent data series were conducted to analyze subjects with OH and subjects without OH (variance analysis and Chi-squared test).

We used a Cox proportional hazard model with delayed entry to study the risk of incident dementia in relation to OH. Because it is difficult to define the date of onset of the dementing process, which is generally insidious, the age of diagnosis of dementia was defined as the age at the midpoint of the interval between the date of diagnosis and the date of the previous visit without dementia. The selected time axis is the age of subject, with delayed entry and left truncation. Participants without dementia were right censored at the end of their last visit or in the event of death. The principal explanatory variable was OH status. Model 1 was a univariate model, uniquely adjusted for the variable center. Model 2 was adjusted for the variables known to be associated with dementia or with OH-ApoE4 status,¹⁹ cognitive state, depression,²⁰ education level,²¹ diabetes mellitus, high blood pressure, cardiovascular history, and center, which were selected during a step-by-step manual procedure, in descending order, using a cohort without missing data to ensure a constant sample size.

A sensitivity analysis was performed using an illness-death model taking into account the competing risk by death and interval censoring.²² The illness-death model is a semiparametric multistate model, which has been designed to take into account properly the competitive risk with death induced by the interval censoring and, thus, avoids bias.²³ Therefore, it incorporates the different transition states applicable to this study.²⁴ The first transition (baseline to dementia) is adjusted for the center, using only univariate analysis, and for the adjustment variables from model 2 of the principal multivariate analysis. The second transition (baseline to death) is adjusted in univariate analysis for sex and center. In the multivariate analysis, the cardiovascular risk factors are introduced into the model. The third transition (dementia to death) is adjusted by default for the variables used in the first transition.

In a second analysis, we explored the potential association of the OH to the 2 main different causes of dementia, which are Alzheimer disease and vascular dementia. Cox proportional hazard models with delayed entry were performed with Alzheimer disease and then vascular dementia as primary outcome. The adjustment variables were taken from model 2 of our primary analysis.

All analyses were performed using SAS v9.4 (SAS Institute, Inc, Cary, NC) except those concerning the illness-death model that used R's smooth-hazard package. A 2-tailed *P* value ≤ 0.05 was considered to be statistically significant.

Results

The initial sample of the Three-City study was composed of 9294 subjects. However, 1745 of the subjects did not have their blood pressure measured in standing position, rendering the diagnosis of OH impossible, and 214 subjects had already been diagnosed with dementia at the start of the study. Our final study sample, therefore, consisted of 7425 participants (Figure). Subjects who had not undergone a standing blood pressure measurement represented $\approx 20\%$ of the total cohort. These subjects were equally represented between the 3 centers. In comparing the general characteristics of these participants with those in the study sample, we observe that the former are a significantly older population group ($P<0.0001$) with an accumulation of cardiovascular risk factors (Table S1 in the [online-only Data Supplement](#)).

Using the conventional significance threshold to diagnose OH, we observe an overall OH in 978 participants (13% of the working sample). With the second definition proposed, numbers are different: mild OH was present in 2411 participants (32%) and severe OH in 330 participants (4.5%).

Participants with OH had an increased cardiovascular risk compared with participants without OH, were older ($P=0.0016$), had a higher proportion of cardiovascular history ($P<0.0001$), and had higher SBP ($P<0.0001$). Distribution of ApoE4⁺ state, cognitive state, and level of education was comparable in the 2 groups (Table 1).

During a mean follow-up of 7.5 years representing 55 539 person-years, 760 cases of dementia were diagnosed. Among these, 304 died during the course of follow-up. The average period between diagnosis of dementia and death was 4.96 years (± 2.26). We recorded 1962 deaths during the study. An association between the OH status and death was observed ($P<0.0001$; Table S2 in the [online-only Data Supplement](#)). OH was associated with an increased risk of $\approx 20\%$ of incident dementia for conventional and mild OH thresholds (Table 2). This association seemed stronger using the severe OH threshold with an increased risk of incident dementia of 54% and 57% in the univariate and multivariate analyses, respectively. Most of these associations were found to be statistically significant.

In the sensitive analysis using the illness-death model, the relative risks of developing dementia were of the same

Table 1. Comparison of the 3C Subjects According to Their OH Status at Baseline, n=7425

Variables	N	Subjects Without OH (n=6447)	Subjects With OH (n=978)	P Value
Age, y, mean (\pm SD)	7425	73.39 (± 4.9)	74.27 (± 5)	<0.0001
Sex (% M)	7425	39.46	42.84	0.0440
BMI, mean (\pm SD)	7414	25.74 (± 4)	25.32 (± 4)	0.0023
SBP, mean (\pm SD)	7425	140.00 (± 20)	150.00 (± 22)	<0.0001
DBP, mean (\pm SD)	7425	80.00 (± 10)	85.00 (± 13)	<0.0001
HR, mean (\pm SD)	7410	67.00 (± 10)	67.50 (± 11)	0.3850
Cardiovascular history, %	7424	8.56	10.73	0.0250
Diabetes mellitus, %	7391	7.40	8.80	0.1060
Hypertension, %	7378	39.70	47.44	<0.0001
Active smoker, %	7379	35.53	32.82	0.1050
Dyslipidemia, %	7315	33.45	39.33	0.0650
Psychotropic medication, %	7425	25.56	26.07	0.7300
Hypotensive medication, %	7425	48.14	59.30	<0.0001
ApoE4, %	7234	20.32	21.72	0.3166
Cognitive status, %	7341	4.69	4.11	0.4210
Depression, %	7396	13.02	14.92	0.1040
Education, %	7412	24/36/20/20	24/35/22/19	0.9015

Cardiovascular history was defined as acute coronary syndrome, myocardial revascularization, and stroke; Diabetic status was defined by a level of fasting blood glucose >7 mmol/L or the intake of antidiabetic treatment (oral treatment or insulin); Dyslipidemia was defined by a cholesterol level >5.2 mmol/L or a hypolipidemic treatment; and Depression was defined by a CESD score of >16 for men and >23 for women. % indicates proportion; 3C, Three-City study; BMI, body mass index; CESD, Center for Epidemiology Studies-Depression; DBP, diastolic blood pressure in mm Hg; HR, heart rate per minute; M, male; SBP, systolic blood pressure in mm Hg; and SD, standard deviation.

order of magnitude as in the Cox proportional hazard model (Table 2), regardless of the definition of OH.

In our second analysis, according to dementia pathogenesis (Alzheimer or vascular), we noted 512 incident Alzheimer cases, and 151 incident vascular dementia represented 87% of the overall incident dementia. The Cox regression analysis after adjustment did not show a significant association between OH and Alzheimer disease (hazard ratio, 1.19; 95% confidence interval, 0.91–1.57; $P=0.212$) and between OH and vascular dementia (hazard ratio =1.42; 95% confidence interval, 0.92–2.15; $P=0.111$), respectively.

Discussion

In the Three-City study, OH at baseline was associated with an increased risk of incident dementia during the 12 years of follow-up. This association is not explained by the initial differences in the distribution of risk factors of dementia because no significant differences were observed between the populations with and without OH, in terms of cognitive state ($P=0.42$), depression score ($P=0.10$), education level ($P=0.90$), and ApoE4⁺ status ($P=0.31$).

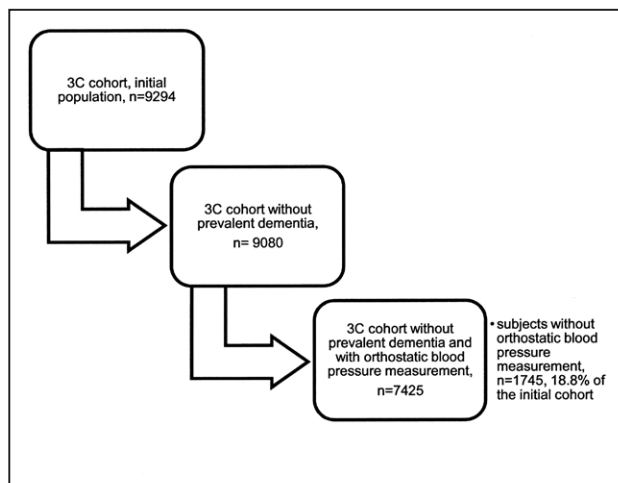


Figure. Flow chart of selection of participants from the Three-City (3C) study cohort.

Table 2. Results From the Univariate and Multivariate Analyses of the Risk of Incident Dementia at 12 Years of Follow-Up

Variable of Interest	Model 1 (n=7129)			Model 2 (n=6773)		
	HR	95% CI	PValue	HR	95% CI	PValue
OH* (n=117)						
Cox	1.19	0.98–1.46	0.0783	1.23	1.01–1.51	0.0457
ID model	1.26	1.03–1.53	0.0244	1.24	1.02–1.52	0.0412
Mild OH* (n=278)						
Cox	1.20	1.04–1.40	0.0149	1.23	1.05–1.43	0.0086
ID model	1.23	1.06–1.43	0.0074	1.23	1.05–1.43	0.0086
Severe OH* (n=46)						
Cox	1.54	1.15–2.08	0.0043	1.57	1.15–2.14	0.0043
ID model	1.51	1.11–2.04	0.0077	1.51	1.12–2.04	0.0077

Cox analysis compared with illness-death model of the Three-City study cohort, n=7425. For Cox analysis: Model 1, adjusted for center; Model 2, adjusted for center, diabetes mellitus, cardiovascular history, hypertension, APOE4⁺ status, education, depression, and cognitive status. For illness-death model (ID-model): Model 1, transition 0–1 (baseline to dementia) adjusted for center; transition 0–2 (baseline to death) adjusted for sex and center; Model 2, transition 0–1 adjusted for center, diabetes mellitus, cardiovascular history, hypertension, APOE4⁺ status, education, depression, and cognitive status.

OH: drop of >20 mm Hg for SBP or >10 mm Hg for DBP; mild OH: drop of >10 mm Hg for SBP or >5 mm Hg for DBP; and severe OH: drop of >30 mm Hg for SBP or >15 mm Hg for DBP. CI indicates confidence interval; HR, hazard ratio; ID, illness-death; and OH, orthostatic hypotension.

*Incident dementia with OH.

Atrial fibrillation is another factor which has been described as associated to dementia.²⁵ However, in our study sample, if we noticed a slightly significant higher frequency of atrial fibrillation in subject with OH (3.46% versus 2.30%; $P=0.0372$), atrial fibrillation was not associated to incident dementia (hazard ratio, 1.18; 95% confidence interval, 0.71–1.895; $P=0.503$). Furthermore, the higher the prominence of OH, the stronger the association, with an increased risk of dementia of 50% observed for severe OH. Similar results were found in the sensitivity analysis with a dedicated method,²³ which reinforces the strength of the association.

Blood pressure drop in standing position is a marker of autonomic dysfunction and may lead to increased BP variability. Blood pressure variability has been studied through several markers: visit-to-visit variability, variability for 24H, and home blood pressure variability. The association of all of these markers with the increased incidence of cardiovascular events has been proven.²⁶ To date, visit-to-visit variability is the only marker able to predict incident dementia as a long-term marker of variability.²⁷ OH, which is a short-term marker of variability, offers additional evidence of the link between blood pressure variability and dementia.

This work, thus, provides new insight on the relationship between blood pressure and dementia. In mid-life adults, high blood pressure is associated with an increased risk of dementia.^{28–30} High blood pressure and different cardiovascular risk factors result in accelerated vascular aging, structurally modifying both large and small arteries. About

the large arteries (the aorta in particular), the wall loses its elastic properties and grows stiffer. This arterial stiffness is accompanied by poorer blood pressure regulation, with an increase in blood pressure variability, and prevalence of OH.³¹ In elderly individuals, we have now evidences²⁷ that it is the blood pressure variability not the blood pressure level which is associated with increased risk of dementia, leading to blood pressure surges accompanied by impaired cerebral microcirculation, most likely responsible for repeated episodes of ischemia.

However, contrary to other markers of blood pressure variability, OH has many causes. OH can be related to an insufficiency of the central regulation system of blood pressure as is the case for neurodegenerative diseases³² (in particular, Parkinson's disease and diabetes mellitus) or to an inadequacy of the peripheral baroreceptors as is the case for vascular aging. Given this complexity, it is difficult to identify whether OH is a pure marker of vascular aging or whether it is an early marker of an ongoing neurodegenerative dementia process. Despite that OH is not more strongly associated to vascular dementia than Alzheimer disease in our second analysis, OH as a vascular aging marker lead seems to be the most likely for several reasons. First, in our cohort, subjects with OH are significantly older ($P<0.0001$), hypertensive ($P<0.0001$), and have a greater proportion of cardiovascular events ($P=0.0250$) than those without OH (Table 1). So, this population with OH has a higher cardiovascular risk than those without. Furthermore, as aforementioned, many studies have shown that OH is a risk factor of cardiovascular events (coronary artery disease, heart failure, and stroke).^{2,33} Otherwise, subjects in the Three-City study centers are screened during each visit to allow early diagnosis of dementia. Therefore, the possibility that OH remains for the years as the only sign of an ongoing dementia process is quite unlikely. Moreover, OH of central origin is generally associated with other dysautonomic signs, such as abnormal heart rate regulation. However, in our study, we did not observe any association between heart rate variability (defined as the difference between lying and standing heart rate) and incident dementia (hazard ratio=1.00; 95% confidence interval, 0.990–1.008; $P=0.783$). Finally, diabetes mellitus is a frequent cause of dysautonomia and OH. However, in our study, there is no significant difference of diabetes mellitus distribution according to OH status ($P=0.1060$; Table 1).

Limitations

About 20% of the population did not have their blood pressure measured in standing position. This group does not have the same characteristics as the study sample (Table 1); in particular, the former is significantly older with a higher cardiovascular risk, thus, with increased risk of dementia and OH. The reasons why some subjects in the study did not have their blood pressure measured in standing position have not been specified in the database, but the proportion of missing data are somewhat similar in each of the 3 cities. This suggests that the reasons behind the lack of blood pressure measurements in standing position by investigators were similar and associated with the condition of patients (subject tiredness and clinical weakness seem evident here).

Our study incorporated a unique way of measuring orthostatism, which did not follow the general consensus on repeating the orthostatism measurements for 3 minutes, which, in turn, undeniably reduced the initial prevalence recorded in our study. Moreover, symptoms induced by OH were not collected at the start of the study. Indeed, symptomatic OH reflects the reality of cerebral hypoperfusion and could be better correlated to the clinical outcome. However, recent data suggest that symptomatic hypotension makes up <10% of OH and does not have a stronger association with occurrence of cardiovascular event than asymptomatic OH.³⁴

These limitations could partially explain the relatively weak prevalence of OH of $\approx 13\%$ compared with other studies. However, this does not question the strength of the association between OH and dementia, which is probably underestimated as a result of these limitations.

An important limitation of the current results is the lack of representativeness of the Three-City study sample. Because the participation rate was $\approx 37\%$,⁹ our sample was, therefore, not representative of the general population, and the association observed might not be true in the general population.

Conclusion and Perspectives

OH, a simple marker of blood pressure variability, is associated with an increased risk of developing dementia of about at least 25%. Thus, it could help to identify subjects with high risk of dementia.

Moreover, it raises the question of the need to take into account blood pressure variability and in particular OH among subjects with high risk of dementia and to test whether reducing OH could reduce the incidence of dementia.

Sources of Funding

The Three-City study is conducted under a partnership agreement among the Institut National de la Santé et de la Recherche Médicale (INSERM), Bordeaux University, and Sanofi-Aventis. The Fondation pour la Recherche Médicale funded the preparation and initiation of the study. It is also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, Mutuelle Générale de l'Éducation Nationale (MGEN), Institut de la Longévité, Conseils Régionaux of Aquitaine and Bourgogne, Fondation de France, and Ministry of Research-INSERM Programme Cohortes et collections de données biologiques. C. Tzourio has received investigator-initiated research funding from the French National Research Agency, the Fondation Leducq, and the Initiative of Excellence (IdEX) of Bordeaux University.

Disclosures

None.

References

- Fedorowski A, Melander O. Syndromes of orthostatic intolerance: a hidden danger. *J Intern Med*. 2013;273:322–335. doi: 10.1111/joim.12021.
- Ricci F, Fedorowski A, Radico F, Romanello M, Tatasciore A, Di Nicola M, Zimarino M, De Caterina R. Cardiovascular morbidity and mortality related to orthostatic hypotension: a meta-analysis of prospective observational studies. *Eur Heart J*. 2015;36:1609–1617. doi: 10.1093/eurheartj/ehv093.
- Passant U, Warkentin S, Karlson S, Nilsson K, Edvinsson L, Gustafson L. Orthostatic hypotension in organic dementia: relationship between blood pressure, cortical blood flow and symptoms. *Clin Auton Res*. 1996;6:29–36.
- Hayakawa T, McGarrigle CA, Coen RF, Soraghan CJ, Foran T, Lawlor BA, Kenny RA. Orthostatic blood pressure behavior in people with mild cognitive impairment predicts conversion to dementia. *J Am Geriatr Soc*. 2015;63:1868–1873. doi: 10.1111/jgs.13596.
- Viramo P, Luukinen H, Koski K, Laippala P, Sulkava R, Kivela SL. Orthostatic hypotension and cognitive decline in older people. *J Am Geriatr Soc*. 1999;47:600–604.
- Elmstahl S, Widerstrom E. Orthostatic intolerance predicts mild cognitive impairment: incidence of mild cognitive impairment and dementia from the Swedish general population cohort Good Aging in Skane. *Clin Interv Aging*. 2014;9:1993–2002. doi: 10.2147/CIA.S72316.
- Yap PL, Niti M, Yap KB, Ng TP. Orthostatic hypotension, hypotension and cognitive status: early comorbid markers of primary dementia? *Dement Geriatr Cogn Disord*. 2008;26:239–246. doi: 10.1159/000160955.
- Rose KM, Couper D, Eigenbrodt ML, Mosley TH, Sharrett AR, Gottesman RF. Orthostatic hypotension and cognitive function: the Atherosclerosis Risk in Communities Study. *Neuroepidemiology*. 2010;34:1–7. doi: 10.1159/00025459.
- 3C Study Group. Vascular factors and risk of dementia: design of the Three-City study and baseline characteristics of the study population. *Neuroepidemiology*. 2003;22:316–325. doi: 10.1159/000072920.
- Barberger-Gateau P, Raffaitin C, Letenneur L, Berr C, Tzourio C, Dartigues JF, Alpérovitch A. Dietary patterns and risk of dementia: the Three-City cohort study. *Neurology*. 2007;69:1921–1930. doi: 10.1212/01.wnl.0000278116.37320.52.
- Jacquin-Gadda H, Fabrigoule C, Commenges D, Letenneur L, Dartigues JF. A cognitive screening battery for dementia in the elderly. *J Clin Epidemiol*. 2000;53:980–987.
- McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34:939–944.
- O'Brien E, Waeber B, Parati G, Staessen J, Myers MG. Blood pressure measuring devices: recommendations of the European Society of Hypertension. *BMJ*. 2001;322:531–536.
- Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The consensus committee of the American Autonomic Society and the American Academy of Neurology. *Neurology*. 1996;46:1470.
- Beckett NS, Connor M, Sadler JD, Fletcher AE, Bulpitt CJ. Orthostatic fall in blood pressure in the very elderly hypertensive: results from the hypertension in the very elderly trial (HYVET) - pilot. *J Hum Hypertens*. 1999;13:839–840.
- Ewing DJ. Diabetic autonomic neuropathy and the heart. *Diabetes Res Clin Pract*. 1996;30(suppl):31–36.
- Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189–198.
- Kneisevich JW, Biggs JT, Clayton PJ, Ziegler VE. Validity of the Hamilton Rating Scale for depression. *Br J Psychiatry*. 1977;131:49–52.
- Limon-Sztencel A, Lipska-Ziętkiewicz BS, Chmara M, Wasag B, Bidzan L, Godlewska BR, Limon J. The algorithm for Alzheimer risk assessment based on APOE promoter polymorphisms. *Alzheimers Res Ther*. 2016;8:19. doi: 10.1186/s13195-016-0187-9.
- Mirza SS, Wolters FJ, Swanson SA, Koudstaal PJ, Hofman A, Tiemeier H, Ikram MA. 10-year trajectories of depressive symptoms and risk of dementia: a population-based study. *Lancet Psychiatry*. 2016;3:628–635. doi: 10.1016/S2215-0366(16)00097-3.
- Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol*. 2012;11:1006–1012. doi: 10.1016/S1474-4422(12)70191-6.
- Leffondré K, Touraine C, Helmer C, Joly P. Interval-censored time-to-event and competing risk with death: is the illness-death model more accurate than the Cox model? *Int J Epidemiol*. 2013;42:1177–1186. doi: 10.1093/ije/dyt126.
- Weuve J, Proust-Lima C, Power MC, Gross AL, Hofer SM, Thiébaud R, Chêne G, Glymour MM, Dufouil C; MELODEM Initiative. Guidelines for reporting methodological challenges and evaluating potential bias in dementia research. *Alzheimers Dement*. 2015;11:1098–1109. doi: 10.1016/j.jalz.2015.06.1885.
- Joly P, Commenges D, Helmer C, Letenneur L. A penalized likelihood approach for an illness-death model with interval-censored data: application to age-specific incidence of dementia. *Biostatistics*. 2002;3:433–443. doi: 10.1093/biostatistics/3.3.433.
- Hui DS, Morley JE, Mikolajczyk PC, Lee R. Atrial fibrillation: a major risk factor for cognitive decline. *Am Heart J*. 2015;169:448–456. doi: 10.1016/j.ahj.2014.12.015.
- Stevens SL, Wood S, Koshiaris C, Law K, Glasziou P, Stevens RJ, McManus RJ. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. *BMJ*. 2016;354:i4098.

27. Alperovitch A, Blachier M, Soumaré A, Ritchie K, Dartigues JF, Richard-Harston S, Tzourio C. Blood pressure variability and risk of dementia in an elderly cohort, the Three-City Study. *Alzheimers Dement*. 2014;10(5 suppl):S330–S337. doi: 10.1016/j.jalz.2013.05.1777.
28. Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, Havlik RJ. Midlife blood pressure and dementia: the Honolulu-Asia aging study. *Neurobiol Aging*. 2000;21:49–55.
29. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology*. 2005;64:277–281. doi: 10.1212/01.WNL.0000149519.47454.F2.
30. Tzourio C, Laurent S, Debet S. Is hypertension associated with an accelerated aging of the brain? *Hypertension*. 2014;63:894–903. doi: 10.1161/HYPERTENSIONAHA.113.00147.
31. Boudaert J, Tamim H, Verny M, Belmin J. Arterial stiffness is associated with orthostatic hypotension in elderly subjects with history of falls. *J Am Geriatr Soc*. 2004;52:568–572. doi: 10.1111/j.1532-5415.2004.52163.x.
32. Ewing DJ, Clarke BF. Autonomic neuropathy: its diagnosis and prognosis. *Clin Endocrinol Metab*. 1986;15:855–888.
33. Mancia G, Grassi G. Orthostatic hypotension and cardiovascular risk: defining the epidemiological and prognostic relevance. *Eur Heart J*. 2010;31:12–14. doi: 10.1093/eurheartj/ehp389.
34. Fleg JL, Evans GW, Margolis KL, Barzilay J, Basile JN, Bigger JT, Cutler JA, Grimm R, Pedley C, Peterson K, Pop-Busui R, Sperl-Hillen J, Cushman WC. Orthostatic hypotension in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) blood pressure trial: prevalence, incidence, and prognostic significance. *Hypertension*. 2016;68:888–895. doi: 10.1161/HYPERTENSIONAHA.116.07474.

Novelty and Significance

What Is New?

- Orthostatic hypotension (OH) is strongly associated with incident dementia.
- This work highlights the particular relationship between blood pressure and brain aging according to the age of the subject.

What Is Relevant?

- Two different statistical methods and different OH thresholds were used in a large cohort of subject with an important follow-up and, therefore, confirmed the strength of the association.

- OH is a common situation, in particular, in old subject, and, thus, could help to identify subjects with a high risk of dementia.

Summary

Because OH is common and easy to measure, OH measurements could help to identify subjects with higher risk of dementia.