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Mathilde Strumia, J S Vidal, Philippe Cestac, Brigitte Sallerin, O. Hanon, Laure Rouch

► **To cite this version:**

Mathilde Strumia, J S Vidal, Philippe Cestac, Brigitte Sallerin, O. Hanon, et al.. Orthostatic hypotension and orthostatic hypertension are both associated with lower cognitive function: The S.AGES cohort. *Journal of the American Geriatrics Society*, 2023, 71 (12), pp.3721-3730. 10.1111/jgs.18571 . hal-04806876

**HAL Id: hal-04806876**

**<https://ut3-toulouseinp.hal.science/hal-04806876v1>**

Submitted on 27 Nov 2024


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# Orthostatic hypotension and orthostatic hypertension are both associated with lower cognitive function: The S.AGES cohort

M. Strumia PharmD, PhD<sup>1,2</sup>   | J. S. Vidal MD, PhD<sup>3,4</sup> |  
P. Cestac PharmD, PhD<sup>1,2</sup> | B. Sallerin PharmD, PhD<sup>2,5</sup> | O. Hanon MD, PhD<sup>3,4</sup> |  
L. Rouch PharmD, PhD<sup>1,2</sup> | for the S.AGES Investigators

<sup>1</sup>Maintain Aging Research Team, CERPOP, Université de Toulouse, Inserm, Université Paul Sabatier, Toulouse, France

<sup>2</sup>Département de pharmacie Clinique, pôle gériatrie, Centre Hospitalier Universitaire de Toulouse, Toulouse, France

<sup>3</sup>EA 4468, Université de Paris, Paris, France

<sup>4</sup>Service de gériatrie, Hôpital Broca, AP-HP, Hôpitaux Universitaires Paris Centre, Paris, France

<sup>5</sup>RESTORE UMR 1301, Inserm 5070, CNRS EFS, équipe FLAMES, Université Paul Sabatier, Toulouse, France

## Correspondence

M. Strumia, CHU de Toulouse, Department of Clinical Pharmacy, 330 Avenue de Grande Bretagne, 31300 Toulouse, France.  
Email: [strumia.m@chu-toulouse.fr](mailto:strumia.m@chu-toulouse.fr)

## Abstract

**Background:** Blood pressure (BP) postural changes, both orthostatic hypotension (OHYPO) and orthostatic hypertension (OHYPER) are common in older adults. Few studies have investigated their association with cognition, particularly for OHYPER, an emerging cardiovascular risk factor. We aimed to assess the association between OHYPO, OHYPER and cognition in non-institutionalized older subjects.

**Methods:** The S.AGES (Sujets ÂGES, Aged Subjects) cohort followed every 6 months for 3 years non-institutionalized subjects aged  $\geq 65$  years without dementia at inclusion, in France. OHYPO and OHYPER were respectively defined as a fall or an increase of  $\geq 20$  mmHg in systolic BP and/or  $\geq 10$  mmHg in diastolic BP after standing from a sitting position. Cognition was assessed using the Mini-Mental State Examination (MMSE). Linear mixed models were used for the analyses.

**Results:** Among the 3170 subjects included (mean age 78 years, 56% women), 209 (6.5%) had OHYPO and 226 (7.1%) had OHYPER at baseline. After adjustment for demographics, cardiovascular risk factors and disease, seated SBP/DBP and BP lowering treatment, mean MMSE was 0.52 point lower in participants with OHYPER compared to those with normal BP postural

Linda Benattar-Zibi (Directeur Médical ORPEA), Philippe Bertin (Centre Hospitalier Universitaire de Limoges, Rhumatologie, Limoges, France), Gilles Berrut (Centre Hospitalier Universitaire de Nantes, Pôle de soins gériatriques, Nantes, France), Emmanuelle Corruble (Université Paris-Saclay, AP-HP, Service de Psychiatrie, Hôpital de Bicêtre, DMU 11 Psychiatrie, Santé Mentale, Addictologie et Nutrition, Équipe MOODS, Inserm U1178, CESP [Centre de Recherche en Épidémiologie et Santé des Populations], Le Kremlin-Bicêtre, France), Geneviève Derumeaux (Université Paris Est Créteil [UPEC], FHU SENE, IMRB, INSERM, Créteil, France, Département de Physiologie-Explorations Fonctionnelles, Hôpitaux Universitaires Henri Mondor, AP-HP, Avenue Maréchal de Lattre de Tassigny, Créteil, France), Bruno Falissard (Département de biostatistiques, CESP, Université Paris-Saclay, UVSQ, AP-HP, Paris, France), Françoise Forette (Université René Descartes, Fondation Nationale de Gérontologie, Paris, France), Florence Pasquier (Centre Hospitalier Universitaire de Lille, Neurologie, Lille, France), Michel Pinget (Service de gériatrie, Hôpital Broca, AP-HP, Hôpitaux Universitaires Paris Centre, Paris, France), Rissane Ourabah (Département de Médecine Générale, Université de Paris-Saclay, Paris, France), Nicolas Danchin (Service de Cardiologie, Hôpital Européen Georges Pompidou)

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changes ( $\beta$  adjusted [95% CI] =  $-0.52$  [ $-0.96$ ;  $-0.09$ ],  $p = 0.02$ ) and 0.50 point lower in participants with OHYPO compared to those with normal BP postural changes ( $\beta$  adjusted [95% CI] =  $-0.50$  [ $-0.95$ ;  $-0.06$ ],  $p = 0.03$ ). Sensitivity analyses showed a dose–response relationship between OHYPO and cognition.

**Conclusion:** Although the absolute differences in MMSE were small, both OHYPO and OHYPER were associated with lower cognition. Orthostatic BP measurements could help identify patients with risk of cognitive impairment. Further studies are needed to assess whether controlling orthostatic BP could be a promising interventional target in preserving cognition among older adults.

#### KEYWORDS

blood pressure, cognition, older people, orthostatic hypertension, orthostatic hypotension

## INTRODUCTION

Cognitive impairment and dementia represent a major public health concern because of global increase in population size and life expectancy. From a preventive standpoint, identification of potentially modifiable risk factors is critically important.

Postural changes in blood pressure (BP) affect until 30% of older adults<sup>1–4</sup> and several pharmacological and non-pharmacological interventions may improve orthostatic symptoms.<sup>5</sup> Over the past decade, orthostatic hypotension (OHYPO) has been suggested to be associated with an increased risk of cardiovascular and all-cause mortality<sup>6</sup>; yet, less is known about OHYPO and cognitive outcomes.<sup>7–12</sup> In contrast to OHYPO, BP may rise when standing in some individuals, possibly as a result of overcompensation for the gravitational challenge.<sup>13</sup> This phenomenon, called orthostatic hypertension (OHYPER), has been increasingly recognized as an emerging cardiovascular risk factor.<sup>14,15</sup> Only very few studies have explored its association with cognitive function and have shown inconsistent findings.<sup>8,16,17</sup> Limited follow-up, insufficient number of participants, inconsistencies in cognitive assessment, and different thresholds to define BP postural changes could explain these conflicting results.

Thus, in order to fill the gap in the existing literature, we aimed to investigate the association between OHYPO, OHYPER and cognitive function in the prospective S. AGES (Sujets Âgés) cohort of non-institutionalized patients aged  $\geq 65$  years and followed-up for 3 years.

## METHODS

### Study population

The S. AGES (Sujets Âgés – Aged Subjects)<sup>18</sup> cohort is a multi-center prospective observational study of 3491 non-

### Key points

- Our findings suggest that orthostatic hypotension and orthostatic hypertension were both associated with lower cognitive performance.
- A significant dose–response relationship was found between OHYPO and lower cognitive function.
- Orthostatic blood pressure measurements could help to identify patients with greater risk of cognitive impairment.

### Why does this paper matter?

Postural changes in blood pressure, which affect up to 20%–30% of older adults, can be easily detected in clinical practice. In addition, several pharmacologic and non-pharmacologic interventions may improve orthostatic symptoms. Our findings showing an association between OHYPO, OHYPER, and lower cognitive function, are of critical importance to identify patients with greater risk of cognitive impairment and possibly implement preventive strategies.

institutionalized patients aged 65 years and over, conducted in France between 2009 and 2014. Patients were recruited and followed-up by their general practitioner every 6 months for 3 years. The methodology and study design have been described elsewhere.<sup>18</sup> The primary objective of the S. AGES cohort was to describe the real-life therapeutic care of older people. The S. AGES cohort consisted of three sub-cohorts of patients with either: type 2 diabetes (T2DM) ( $n = 1004$ ), chronic pain ( $n = 1400$ ), or atrial fibrillation (AF) ( $n = 1087$ ). The inclusion criteria were being 65 years and older, living in

France, being covered by the national health insurance and having chronic pain, T2DM or AF. The exclusion criteria were being resident of a nursing home, unable to give consent and to take part in the follow-up procedures, participating in another clinical trial, and presenting a life-threatening disease with <3-month life expectancy. All patients gave and signed an informed consent to participate in the study. The protocol was approved by the local ethics committee and was in accordance with institutional guidelines and criteria of the Declaration of Helsinki. The study has been registered on the [clinicaltrials.gov](https://clinicaltrials.gov) website to the number NCT01065909.

## Assessment of orthostatic BP changes

Given that older adults often have comorbid conditions that may affect mobility and have a higher risk of falls,<sup>16</sup> sit-to-stand measures, which offer a safer method to assess BP postural changes, were used in the S.AGES cohort, in accordance with previous studies.<sup>15,16,19</sup> Systolic BP (SBP) and diastolic BP (DBP) were measured once at baseline by general practitioners as part of the routine clinical care, after at least 10 min of rest, in a seated position on the left arm using a validated electronic device (OMRON 750 CP; Omron Healthcare, Co., Ltd., Kyoto, Japan). A new measure was taken in the standing position after 3 min. OHYPO was defined as a decrease in SBP of at least 20 mmHg and/or a decrease in DBP of at least 10 mmHg<sup>20</sup> after postural change. In the absence of consensus, OHYPER was defined according to the most common definition used in the literature,<sup>17,21–25</sup> as a rise of SBP of at least 20 mmHg and/or a rise of DBP of at least 10 mmHg after postural change.

## Assessment of cognitive function

Dementia was assessed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth revision.<sup>26</sup> All participants were dementia-free at baseline.

Global cognitive performances were measured at baseline and annually by general practitioners using the Mini-Mental State Examination (MMSE).<sup>27</sup> The MMSE (maximum score of 30 points, higher indicating better performance) measures 7 cognitive domains: orientation in time (5 points) and place (5 points), 3-word registration (3 points), attention and calculation (5 points), 3-word recall (3 points), language (8 points), and visual construction (pentagon copying, 1 point). This test is the most widely used in the literature to detect mild cognitive impairment,<sup>28</sup> although the American Academy of Neurology does not recommend a particular tool.<sup>29</sup>

## Statistical analyses

Distributions of continuous variables were presented as mean (standard deviation (SD)). Counts and proportions were used for categorical variables. Baseline characteristics were compared in patients with OHYPO or OHYPER and normal BP postural changes with Student tests for continuous variables and  $\chi^2$  or Fisher's exact tests for categorical variables. Linear mixed models with random intercept and slope were used to assess the association between OHYPO, OHYPER and cognition. Interactions OHYPO  $\times$  time and OHYPER  $\times$  time were checked. Unadjusted and multivariable-adjusted models (age, sex, education and baseline smoking, atrial fibrillation (AF), congestive heart failure, transient ischemic attack (TIA) or stroke, coronary artery disease, T2DM, seated SBP and DBP, BP lowering treatment) were provided. BP lowering treatments were defined based on the literature. All antihypertensive drugs classes (beta-blockers, renin angiotensin system blockers, diuretics, calcium channel blockers, and central antihypertensive drugs), alpha-blockers, antipsychotics, tricyclic antidepressants and dopa-therapy were included in the analysis.<sup>30</sup>

The estimated parameters represent the average difference in MMSE between subjects with normal BP postural changes and subjects with OHYPO ( $\beta$  [OHYPO]) and subjects with OHYPER ( $\beta$  [OHYPER]). The model adequacy was checked using Schoenfeld residuals.

Several sensitivity analyses were also performed. First, analyses were conducted with three other thresholds commonly used to define OHYPO and OHYPER: respectively decrease and increase of (1) 15 mmHg in SBP and/or 7 mmHg in DBP, (2) 30 mmHg in SBP and/or 15 mmHg in DBP, (3) 40 mmHg in SBP and/or 20 mmHg in DBP. Estimated marginal means were used for graphic representations of cognitive performances at 3 years. Second, linear mixed models were provided after MMSE transformation (R package "NormPsy"), given the curvilinearity of this test.<sup>31,32</sup> Third, as the accuracy of BP measurement may be problematic in subjects with AF and because T2DM is a risk factor for dysautonomia, we performed sensitivity analyses after (1) exclusion of participants with baseline AF and (2) exclusion of participants with baseline T2DM. All analyses were performed using R version 3.6.1. A 2-tailed  $p$  value  $\leq 0.05$  was considered statistically significant.

## RESULTS

### Baseline characteristics of the population

Among the 3491 subjects from the S.AGES cohort, 316 (9.1%) had missing baseline BP measurements, and 5 (0.1%) had both OHYPO and OHYPER (in which SBP and DBP change in opposite directions in postural

TABLE 1 Baseline characteristics of the population according to BP postural changes.

	<b>OHYPO</b> ( <i>n</i> = 209, 6.6%)	<b>OHYPER</b> ( <i>n</i> = 226, 7.1%)	<b>Normal BP</b> <b>postural changes</b> ( <i>n</i> = 2735, 86.3%)	<b>OHYPO vs</b> <b>Normal</b> <b>BP postural</b> <b>changes,</b> <i>p</i> -value <sup>b</sup>	<b>OHYPER vs</b> <b>Normal</b> <b>BP postural</b> <b>changes,</b> <i>p</i> -value <sup>b</sup>
	<i>n</i> (%) <sup>a</sup>	<i>n</i> (%) <sup>a</sup>	<i>n</i> (%) <sup>a</sup>		
Age (years), mean (±SD)	79.1 (±6.3)	77.6 (±6.0)	78.1 (±6.3)	<b>0.029</b>	0.218
Female	131 (62.7)	123 (54.7)	1530 (55.9)	0.058	0.711
High school diploma or university	37 (17.8)	44 (19.8)	532 (19.6)	0.521	0.941
MMSE, mean (±SD)	26.2 (±3.7)	26.4 (±4.0)	26.9 (±3.3)	<b>0.008</b>	0.062
Tobacco	209	223	2725	0.735	0.218
Current smoker	6 (2.9)	4 (1.8)	90 (3.3)		
Former or no smoker	203 (97.1)	219 (98.2)	2635 (96.7)		
Coronary artery disease	23 (11.0)	22 (9.7)	289 (10.6)	0.843	0.695
Atrial fibrillation	92 (44.0)	100 (44.2)	1019 (37.3)	0.052	<b>0.037</b>
Heart failure	32 (15.3)	30 (13.3)	347 (12.7)	0.275	0.799
Stroke/TIA	20 (9.6)	16 (7.1)	184 (6.7)	0.119	0.839
Type 2 diabetes	73 (34.9)	98 (43.4)	1102 (40.3)	0.127	0.366
High blood pressure	180 (86.1)	181 (80.4)	2158 (79.1)	<b>0.016</b>	0.642
Antihypertensive treatment	151 (73.0)	164 (73.2)	1910 (70.1)	0.395	0.332
Other BP lowering treatments <sup>c</sup>	20 (10.3)	22 (10.1)	285 (10.8)	0.936	0.861
SBP sitting, mean (±SD)	137.4 (±14.9)	131.7 (±12.1)	133.5 (±11.3)	<b>&lt;0.001</b>	<b>0.031</b>
SBP standing, mean (±SD)	130.0 (±14.8)	139.2 (±13.9)	132.5 (±11.3)	<b>0.020</b>	<b>&lt;0.001</b>
DBP sitting, mean (±SD)	80.0 (±7.6)	71.4 (±7.9)	77.2 (±7.4)	<b>&lt;0.001</b>	<b>&lt;0.001</b>
DBP standing, mean (±SD)	70.1 (±7.0)	82.1 (±7.6)	77.2 (±7.3)	<b>&lt;0.001</b>	<b>&lt;0.001</b>

Note: Bold values are significant values ( $p < 0.05$ ).

Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; high blood pressure, BP greater than 140/90 mmHg or antihypertensive treatment use; m, mean; MMSE, Mini-Mental State Examination score; OHYPER, orthostatic hypertension; OHYPO, orthostatic hypotension; SBP, systolic blood pressure; SD, standard deviation; TIA, transient ischemic attack.

<sup>a</sup>Unless otherwise specified.

<sup>b</sup>Student tests for continuous variables and  $\chi^2$  or Fisher's exact tests for categorical variables.

<sup>c</sup>Alpha-blockers, antipsychotics, tricyclic antidepressants and dopa-therapy.

changes when standing). A total of 3170 individuals (mean age 78 years, 43.7% male) were thus included in our study.

Baseline characteristics of the population are presented in Table 1. Two hundred and nine (6.6%) participants had OHYPO and 226 (7.1%) had OHYPER. Participants with OHYPO were on average older ( $p = 0.03$ ) and had more hypertension ( $p = 0.02$ ) than subjects with normal BP postural changes. Participants with OHYPER had a higher BMI ( $p = 0.02$ ) compared with those with normal BP postural changes, and had more often AF ( $p = 0.04$ ).

BP measurements at baseline were significantly different between the three groups. On average, subjects with OHYPO and OHYPER had respectively higher and

lower sitting SBP and DBP than those with normal BP postural changes ( $p < 0.01$ ).

At baseline, participants with OHYPO had significantly lower MMSE than those with normal postural changes (26.2 vs 26.9,  $p < 0.01$ ). Similar pattern was observed in subjects with OHYPER (26.4 vs 26.9,  $p = 0.06$ ).

### Association between BP postural changes and cognitive function

The association between OHYPER, OHYPO and cognitive function is presented in Tables 2 and 3, respectively. No interactions with time were found between OHYPO ( $\beta = 0.01$ ,  $p = 0.58$ ), OHYPER ( $\beta = 0.01$ ,  $p = 0.22$ ), and

**TABLE 2** Association between OHYPER and cognitive function in unadjusted and multivariate adjusted models.

	$\beta$	[95% CI]	<i>p</i> -value
Model 1 <sup>a</sup>	-0.50	[-0.95; -0.05]	<b>0.028</b>
Model 2 <sup>b</sup>	-0.44	[-0.87; -0.02]	<b>0.042</b>
Model 3 <sup>c</sup>	-0.52	[-0.96; -0.09]	<b>0.017</b>

Note: Bold values are significant values ( $p < 0.05$ ).  $n = 2961$  subjects.

<sup>a</sup>Model 1: univariate linear mixed model with random intercept and slope.

<sup>b</sup>Model 2: Model 1 + adjustment for age at inclusion (years), sex, educational level.

<sup>c</sup>Model 3: Model 2 + coronary artery disease + atrial fibrillation + heart failure + stroke/transient ischemic attack + type 2 diabetes + smoking + SBP sitting (mmHg), DBP sitting (mmHg) + antihypertensive treatment and others BP lowering treatments.

**TABLE 3** Association between OHYPO and cognitive function in unadjusted and multivariate adjusted models.

	$\beta$	[95% CI]	<i>p</i> -value
Model 1 <sup>a</sup>	-0.71	[-1.17; -0.25]	<b>0.002</b>
Model 2 <sup>b</sup>	-0.61	[-1.05; -0.18]	<b>0.006</b>
Model 3 <sup>c</sup>	-0.50	[-0.95; -0.06]	<b>0.026</b>

Note: Bold values are significant values ( $p < 0.05$ ).  $n = 2944$  subjects.

<sup>a</sup>Model 1: univariate linear mixed model with random intercept and slope.

<sup>b</sup>Model 2: Model 1 + adjustment for age at inclusion (years), sex, educational level.

<sup>c</sup>Model 3: Model 2 + coronary artery disease + atrial fibrillation + heart failure + stroke/transient ischemic attack + type 2 diabetes + smoking + SBP sitting (mmHg), DBP sitting (mmHg) + antihypertensive treatment and others BP lowering treatments.

cognitive function. In unadjusted models, both participants with OHYPO or OHYPER had lower cognition compared with those with normal BP postural changes ( $p < 0.03$ ) and this difference was constant over time. After adjustment for demographics, smoking, AF, congestive heart failure, TIA or stroke, coronary artery disease, T2DM, seated SBP and DBP, BP lowering treatment, mean MMSE was 0.52 point lower in participants with OHYPER compared with those with normal BP postural changes ( $\beta$  adjusted [95% CI] = -0.52 [-0.96; -0.09],  $p = 0.02$ ), and this difference was constant over time. Similar results were observed with OHYPO ( $\beta$  adjusted [95% CI] = -0.50 [-0.95; -0.06],  $p = 0.03$ ).

A significant dose-response relationship between OHYPO and cognitive function was found in adjusted linear mixed models (Table 4). The difference in MMSE between participants with OHYPO and with normal BP postural changes was greater at the 40-20 mmHg threshold ( $\beta$  adjusted [95% CI] = -2.38 [-4.28; -0.47],  $p = 0.01$ ) than at the 15-7 mmHg threshold ( $\beta$  adjusted [95% CI] = -0.44 [-0.85; -0.04],  $p = 0.03$ ). A trend was

observed between OHYPER and lower cognition in terms of dose-response relationship. Cognitive performances estimated at 3 years of individuals with and without orthostatic hypotension or hypertension are presented in Figure 1.

In a sensitivity analysis using an MMSE transformation, the mean difference in MMSE between participants with OHYPO ( $p = 0.02$ ) or OHYPER ( $p = 0.02$ ) and participants with normal BP postural changes was significant and constant over time. Results were similar after exclusion of patients with T2DM at baseline (Supplementary Data S1, Supplementary Table S2). After exclusion of participants with AF at baseline, only OHYPER was significantly associated with lower cognitive performances ( $\beta$  adjusted [95% CI] = -0.65 [-1.23; -0.08],  $p = 0.03$ , Supplementary Data S1, Supplementary Table S1).

## DISCUSSION

In our population of non-institutionalized patients aged 65 years and over, OHYPO, but also, very interestingly OHYPER were significantly associated with poorer cognitive function. This relationship was independent of demographics, cardiovascular risk factors, BP lowering treatment and comorbidities. An association was found between OHYPO and lower cognitive function in several cohorts.<sup>7,11,12</sup> Using data from 240 community-dwelling older adults aged 70-79 years old, the Health ABC Study<sup>11</sup> reported an increased risk of dementia in participants with a decreased average systolic orthostatic blood pressure response. Consistent with our findings, a dose-response relationship between OHYPO and incident dementia was found in the Three-City Study.<sup>10</sup> Very few studies investigated the association between OHYPER and cognitive function and showed inconsistent findings. Curreri et al.<sup>8</sup> showed that OHYPER but not OHYPO was associated with cognitive decline in the Progetto Veneto Anziani Study. On the contrary, in the Maine Syracuse Longitudinal Study<sup>16</sup> participants with systolic OHYPO but not OHYPER had lower cognition compared to those with normal postural BP changes. Only one study<sup>17</sup> reported an association between both OHYPO or OHYPER and lower verbal fluency. Furthermore, to our knowledge, our study is the first to show a significant risk of decreased global cognitive performance with both OHYPO and OHYPER participants.

Several mechanisms have been proposed to explain the association between OHYPO, OHYPER and lower cognition. OHYPO is associated with decreased baroreceptor sensitivity and noradrenaline secretion whose role is important to restore BP levels during the transition to a

TABLE 4 Dose–response relationship between OHYPO, OHYPER, and cognitive function.

Orthostatic hypotension				Orthostatic hypertension			
Threshold <sup>a</sup>	$\beta^b$	[95% CI]	<i>p</i> -value	Threshold <sup>a</sup>	$\beta^b$	[95% CI]	<i>p</i> -value
15–7 mmHg	–0.44	[–0.85; –0.04]	<b>0.033</b>	15–7 mmHg	–0.57	[–0.99; –0.16]	<b>0.007</b>
20–10 mmHg	–0.50	[–0.95; –0.06]	<b>0.026</b>	20–10 mmHg	–0.52	[–0.96; –0.09]	<b>0.017</b>
30–15 mmHg	–1.89	[–3.01; –0.78]	<b>0.001</b>	30–15 mmHg	–0.70	[–1.67; 0.27]	0.155
40–20 mmHg	–2.38	[–4.28; –0.47]	<b>0.015</b>	40–20 mmHg	–1.07	[–2.33; 0.20]	0.098

Note: Bold values are significant values ( $p < 0.05$ ). Number of subjects: OHYPO 15–7 mmHg ( $n = 251$  subjects), OHYPO 20–10 mmHg ( $n = 209$  subjects), OHYPO 30–15 mmHg ( $n = 32$  subjects), OHYPO 40–20 mmHg ( $n = 12$  subjects); OHYPER 15–7 mmHg ( $n = 250$  subjects), OHYPER 20–10 mmHg ( $n = 226$  subjects), OHYPER 30–15 mmHg ( $n = 41$  subjects), OHYPER 40–20 mmHg ( $n = 24$  subjects).

<sup>a</sup>Threshold used to define orthostatic hypotension or orthostatic hypertension: respectively decrease or increase of 15 mmHg in systolic blood pressure (SBP) and/or 7 mmHg in diastolic blood pressure (DBP), 20 mmHg in SBP and/or 10 mmHg in DBP, 30 mmHg in SBP and/or 15 mmHg in DBP, or 40 mmHg in SBP and/or 20 mmHg in DBP.

<sup>b</sup>Mixed model with random intercept and slope, adjusted for age, sex, educational level, tobacco, atrial fibrillation, heart failure, cerebrovascular accident, diabetes, antihypertensive drugs and others treatments that may affect blood pressure and sitting blood pressure.

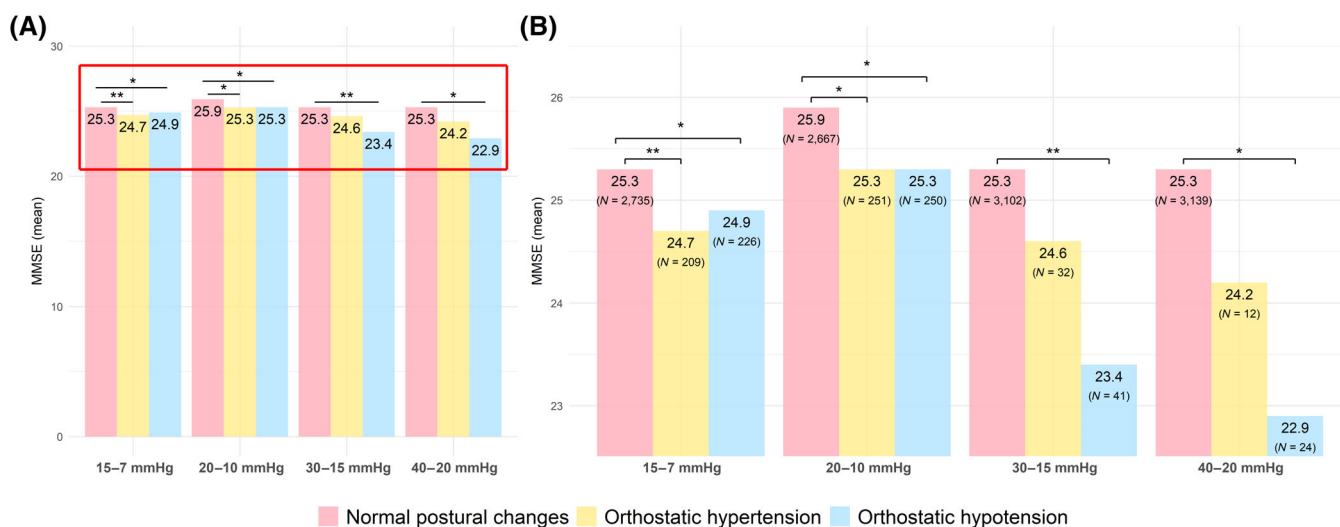


FIGURE 1 Cognitive performances at 3 years according to OHYPO or OHYPER. Average global cognitive performance of individuals with or without orthostatic hypotension or hypertension defined by several thresholds, and after adjustment for age, sex, educational level, tobacco, atrial fibrillation, heart failure, cerebrovascular accident, diabetes, antihypertensive drugs and others treatments that may affect blood pressure and sitting blood pressure. (A) Results with the full range of MMSE scores (0–30). (B) Results focus on average MMSE results. \* $p < 0.05$ ; \*\* $p < 0.01$ .

standing position. OHYPO may promote recurrent transient cerebral hypoperfusion<sup>24,25,33</sup> and repeated episodes of cerebral hypoperfusion could in turn induce hypoxia, promoting neuro-inflammatory and oxidative stress.<sup>34</sup> In patients with OHYPER, a baroreceptor over-response as well as an excessive secretion of vasopressin may partly explain the BP variations. Several studies showed that OHYPER could be a risk factor for cerebral ischemic injury.<sup>35</sup> OHYPO and OHYPER may also lead to shear stress on the vascular wall, causing endothelial injury, micro-vascular damage, and arterial remodeling. These lesions in cerebral vessels may compromise blood–brain barrier permeability and lead to protein extravasation in the cerebral parenchyma.<sup>36,37</sup> Repeated episodes of tissue

hypoxia-ischemia due to both OHYPO and OHYPER could lead to cerebral small vessel disease. Abnormal BP postural changes have been associated with white matter lesions, microbleeds, silent infarcts and brain atrophy, which may partly explain the association between OHYPO, OHYPER and lower cognition. Arterial stiffness could also be a key factor in the relationship between abnormal BP postural changes and cognitive decline. Recent studies have reported an association between OHYPO, OHYPER and stiffness of the large elastic arteries.<sup>38</sup> Arterial stiffness could also damage the cerebral autoregulatory BP system, favoring hypoperfusion episodes. Increasing evidence suggested an association between arterial stiffness and cognitive function.<sup>39</sup>

Finally, the causality of the association between BP postural changes and cognitive function remains poorly understood. The relationship between orthostatic changes in BP and brain damage might be bidirectional. Autonomic dysfunction is very common in patients with dementia, especially in  $\alpha$ -synucleinopathies.<sup>40</sup> In addition, various central nervous system structures affected in Alzheimer's disease are also implicated in autonomic nervous system regulation, such as hypothalamus, locus coeruleus, cerebral neocortex, insular cortex and brain stem.<sup>41</sup> It has been hypothesized that the deficit in central cholinergic function observed in Alzheimer's disease could lead to autonomic dysfunction.<sup>42</sup> BP postural changes can result from decreased sensitivity of the peripheral baroreceptors, decreased activation of the sympathetic nervous system or increased arterial stiffness.<sup>43</sup> However, changes in brain structure related to dementia could contribute to neurovascular instability, BP dysregulation and possibly OHYPO and OHYPER.<sup>44</sup> Further studies are needed to explore mechanisms of the relationship between orthostatic changes in BP and cognition.

Our study has some limitations that are worth noting. First, our findings are based on an observational study, and residual confounding factors may still exist despite extensive efforts to account for possible confounders. Although stratified analyses according to T2DM and AF reported consistent findings, inclusion criteria (subcohorts of patients with either T2DM, AF, or chronic pain) might have limited the generalizability of the results. Second, each general practitioner included between two and five patients, which could induce a potential selection bias among their entire patient population. Third, MMSE was used to assess global cognitive function. Although it is one of the most widely used first-line screening tool for cognitive impairment and can be easily performed by general practitioners, it does not enable the exploration of different cognitive domains. Fourth, measuring orthostatic BP from a seated (instead of lying) to standing position and after 3 min instead of 1 min<sup>45,46</sup> may have blunted the full gravitational effect of postural changes. BP measurements were also done once in each position (seating and standing). This could explain the low prevalence of OHYPO and OHYPER in our population, although other studies have found similar prevalence in community-dwelling older adults.<sup>17,45</sup> Fifth, study duration was only 3 years, which might explain the absence of interaction with time in our models. With a longer period of follow-up, we might have possibly seen, not only a lower cognition but also a pronounced decline over time in older adults with OHYPO and OHYPER. Sixth, such as most of previous studies, heart rate response to orthostatic challenge was not measured. We were not able to distinguish neurogenic from

non-neurogenic OHYPO/OHYPER. Seventh, unlike previous studies, symptoms associated with OHYPO or OHYPER were not recorded, although they may reflect cerebral hypoperfusion. Eighth, we found only a 0.5 point difference in MMSE on average between the groups, although this value is increased to 2.4 points when using the 40–20 mmHg thresholds to define OHYPO. This difference is similar to those found in previous studies using comparable methodology.<sup>8,12</sup> Because of the curvilinearity of this neuropsychological test,<sup>47</sup> a 1-point loss in the higher range of MMSE represents a more severe cognitive impairment than a 1-point loss in the lower range. Thus, we believe that our findings, in a population with a mean MMSE 26.8, are in favor of a clinically meaningful effect of BP postural changes on cognition.

Nevertheless, our study has several strengths. It was conducted on a large sample size of community-dwelling older adults, whereas most studies have been performed in specific populations of patients at high risk of cardiovascular disease or in subjects with dysautonomia. The cohort was well characterized, enabling us to control for important potential confounders. Seated and standing BP measurements were done by general practitioners, minimizing imprecision and bias. We considered normal BP postural changes, OHYPO and OHYPER as separate and exclusive groups whereas most studies pooled participants with either OHYPO or OHYPER and normal BP postural changes. We also assessed the effect of different levels of abnormal BP postural changes on cognitive function using several thresholds to define both OHYPO and OHYPER. We also conducted sensitivity analyses, (1) investigating the effect of BP postural changes on cognitive performances using a validated MMSE transformation accounting for the curvilinearity of the test<sup>31,32</sup> and (2) excluding participants with AF or T2DM. The results were consistent, supporting the robustness of our findings.

## CONCLUSION

In the present study, both OHYPO and OHYPER were associated with lower cognitive performances independently of cardiovascular risk factors and disease, although the absolute differences in MMSE were small. If these associations are confirmed by further studies, regular orthostatic BP monitoring in older adults might help identify individuals at higher risk for cognitive impairment. Promoting an appropriate use of antihypertensive drugs in older people is also critical to prevent orthostatic BP changes; however, further studies are needed to assess whether controlling excessive orthostatic BP changes could be a promising interventional target in preserving cognition among older adults.



## AUTHOR CONTRIBUTIONS

**M. Strumia:** Statistical analysis, analysis and interpretation, draft of the manuscript for important intellectual content. **P. Cestac** and **B. Sallerin:** revision of the manuscript for important intellectual content. **L. Rouch:** feedback and guidance on study design and statistical analysis, analysis and interpretation, revision of the manuscript for intellectual content, supervision. **O. Hanon** and **J. S. Vidal:** acquisition of data, feedback and guidance on study design and statistical analysis, analysis and interpretation, revision of the manuscript for intellectual content, supervision.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

## SPONSOR'S ROLE

This study was financed and sponsored by SANOFI France, which funded general practitioners to include and follow up the S.AGES participants. It also funded the creation of the S.AGES dataset. The present analyses and manuscript writing are completely independent from Sanofi France's funding.

## FINANCIAL DISCLOSURE

No specific funding was received for this work.

## ORCID

M. Strumia  <https://orcid.org/0000-0002-5622-2206>

## TWITTER

M. Strumia  [StrumiaMathilde](#)

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

### **Supplementary Data S1.**

**Supplementary Table S1.** Association between OHYPO, OHYPER, and cognitive function after exclusion of participants with AF.

**Supplementary Table S2.** Association between OHYPO, OHYPER, and cognitive function after exclusion of participants with T2DM.

**Supplementary Figure S3.** Graphical abstract.

**How to cite this article:** Strumia M, Vidal JS, Cestac P, et al. Orthostatic hypotension and orthostatic hypertension are both associated with lower cognitive function: The S.AGES cohort. *J Am Geriatr Soc.* 2023;71(12):3721-3730. doi:[10.1111/jgs.18571](https://doi.org/10.1111/jgs.18571)