Original Article

Blood pressure and cognitive performances in middle-aged adults: the Aging, Health and Work longitudinal study

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Background: Our objective was to investigate the impact of both prevalent and incident hypertension on cognition in middle-aged individuals followed up for 10 years and to explore the extent to which blood pressure control by antihypertensive drugs could modify this relationship.

Method: Three thousand, two hundred and one participants from the Vieillissement Santé Travail (Aging, Health and Work) (VISAT) cohort study, aged 32, 42, 52 and 62 years at baseline were followed up 5 and 10 years later. Blood pressure, antihypertensive medication use as well as memory and speed cognitive performances were assessed at baseline and follow-up. Linear mixed models were used for analyses.

Results: At 10-year follow-up, compared with nonhypertensive participants, prevalent hypertensive individuals showed poorer global cognitive performances ($\beta = -2.99 \pm 0.96$, $P = 0.002$ for participants aged 32 or 42 years at baseline and $\beta = -5.94 \pm 1.00$, $P < 0.001$ for those aged 52 or 62). Patients with incident hypertension had poorer global cognitive performances over time compared with patients without hypertension. When considering prevalent hypertension and blood pressure control status by antihypertensive therapy, untreated and uncontrolled hypertension were associated with poorer cognitive performances than controlled and no hypertension (untreated hypertension compared with no hypertension: $\beta = -5.51 \pm 0.75$, $P < 0.001$; uncontrolled hypertension compared with no hypertension: $\beta = -6.13 \pm 1.40$, $P < 0.001$).

Conclusion: Our findings showed that both prevalent and incident hypertension are associated with poorer global cognitive function in middle-aged individuals and suggested a potential preventive effect of antihypertensive therapy on cognition. Thus, for brain functioning, heightened efforts to detect hypertension and adequately treat it are of critical importance.

Keywords: antihypertensive agent, blood pressure, cognition, epidemiology, hypertension

Abbreviations: BP, blood pressure; DSST, digit symbol substitution subtest; PCA, principal component analysis

INTRODUCTION

Accumulating evidence has suggested that hypertension may be an important risk factor for cognitive decline and dementia [1,2]. However, most studies had a short follow-up, included few participants, only focused on prevalent hypertension, on certain cognitive domains or did not address the potential benefits of antihypertensive therapy [3–10]. They mainly assessed the relationship between late-life or midlife hypertension and cognition in elderly people but few studies evaluated the effect of high blood pressure (BP) on cognitive performances in middle-aged individuals. Thus, the aim of our study was to investigate the impact of both prevalent and incident hypertension on cognitive changes in middle-aged adults followed-up for 10 years. A secondary objective was to explore the extent to which antihypertensive treatment could modify this relationship, particularly with an adequate BP control.

METHODS

Study design and participants

The VISAT study is a 10-year prospective multicenter cohort study aiming to underline the impact of working conditions on health. Details regarding population sampling have been described elsewhere [11]. A total of 4258 current and former salaried workers were randomly selected from

Journal of Hypertension 2018, 36:000–000

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Received 22 February 2018 **Accepted** 7 November 2018

DOI:10.1097/HJH.0000000000002013

the worker's list of 94 occupational physicians in three areas in the South of France. Of these, 3232 participants, aged 32, 42, 52 and 62 years when selected, agreed to participate and were thus included. Recruitment occurred during compulsory medical examinations. Data were collected at three time points in 1996, 2001 and 2006.

Standard protocol approvals, registrations, and patient consents

Participants were informed and volunteered to participate in the study. Oral informed consent was sought and granted. Agreement from the French national committee on computer files and civil liberties (n° 389581V1) was obtained. All the procedures followed the international standards pertaining to human research.

Assessment of hypertension and antihypertensive treatment status

SBP and DBP were measured manually in 1996 and automatically (OMRON 705CP sphygmomanometer) three times at 1-min interval in 2001 and 2006. All BP measurements were done in the office during medical examination by occupational physicians. The average value was used in our analyses. Hypertension was defined as either high BP (mean SBP at least 140 mmHg or mean DBP at least 90 mmHg, according to the current WHO criteria) [12] or current use of antihypertensive medication. Individuals with baseline hypertension were classified as prevalent hypertension. Participants without baseline hypertension, still participating, were classified as incident hypertension if they developed hypertension at 5 or 10-year follow-up. Data regarding antihypertensive medication use were based on self-report of being currently treated for hypertension in 1996, 2001 and 2006. Participants with hypertension were further divided into controlled hypertension (normal BP with medication use), uncontrolled hypertension (high BP despite medication use) and untreated hypertension (high BP without medication use). Participants with normal BP and no medication use represented the reference group.

Assessment of cognitive function

Neuropsychological assessment was performed in 1996, 2001 and 2006 using the same eight cognitive tests each time, administered in the following order: three immediate free recall tests adapted from the Rey auditory verbal learning test [13], the WAIS (Wechsler Adult Intelligence Survey) digit symbol substitution subtest (DSST) [14] considered to be highly loaded by the information processing speed component, two selective attention tests derived from the Sternberg's test [15], a delayed recall test and a recognition test, both based on the material learned earlier.

Assessment of covariates

Age at baseline, sex and educational level were considered as sociodemographic covariates. Sedentary behavior, active smoking, type 1 or 2 diabetes, dyslipidemia, obesity, cardiovascular diseases (myocardial infarction, angina pectoris or stroke), daily alcohol consumption and high social activities level were considered as potential confounding factors. All the collected data were based on self-report, except obesity defined as BMI greater than or equal to 30.

Statistical analyses

A principal component analysis (PCA) was performed to summarize information from the eight cognitive tests [16,17]. Further details are provided in the online-only data supplement, http://links.lww.com/HJH/B44. The first axis was interpreted as a general performance axis whereas the second one tended to contrast memory-oriented tests with speed-oriented tests. A global cognitive performance variable was constructed from this PCA, based on the factorial score of the first axis. Given the structure of the second axis, two additional PCAs, respectively, based on the five memory-oriented tests (three immediate free recalls, one delayed free recall and one delayed recognition measure) and on the three speed-oriented tests (one-digit symbol substitution subtest and two selective attention tests), were performed. Factorial scores instead of standardized means were used in order to maximize the variance summarized by the factorial axes. Linear mixed models were used to analyze cognitive performances over time [18]. Random effects for both intercept and slope were specified. Time-related variables were the measurement occasion and have been considered as dummy variables for the two follow-ups. Interactions prevalent hypertension, incident hypertension or BP control status × measurement occasion were included in our analyses, depending on the predictor used in the model. Interactions prevalent hypertension × age and incident hypertension × age were checked. Our models were adjusted for all potential confounding factors mentioned above, considered as time varying-factors, except for high social activities level because of nonsignificant differences between hypertension groups at baseline. Parameter estimates ($\beta \pm$ SE) gave information about the effect of hypertension and BP control status on cognition. Estimated marginal means were used for graphic representations of cognitive performances. We used the Hochberg method for multiple comparisons [19]. Finally, to test the potential impact of attrition, sensitivity analyses were performed under the hypothesis that participants would be lost to follow-up because of greater decline in cognitive performances over time (see online-only data supplement, http://links.lww.com/HJH/B44). All statistical analyses were performed using STATA software version 15 (Stata Corp, College Station, Texas, USA).

RESULTS

Our baseline sample consisted of 3201 individuals (mean age: 44.9 years ± 10.3). One thousand, five hundred and fifty-nine (48.7%) were women. One thousand and ninety (34%) participants had baseline hypertension and were thus classified as prevalent hypertension. Among the 2111 individuals without baseline hypertension, 350 (16.6%) still participating were classified as incident hypertension at 5 or 10-year follow-up. Figure 1 shows the study flowchart.

Individuals with prevalent hypertension had significantly higher BP [SBP: 145 ± 13 vs. 121 ± 9 mmHg ($P < 0.001$) and DBP: 87 ± 10 vs. 73 ± 8 mmHg ($P < 0.001$)] than individuals without prevalent hypertension. Baseline characteristics of participants according to prevalent hypertension and

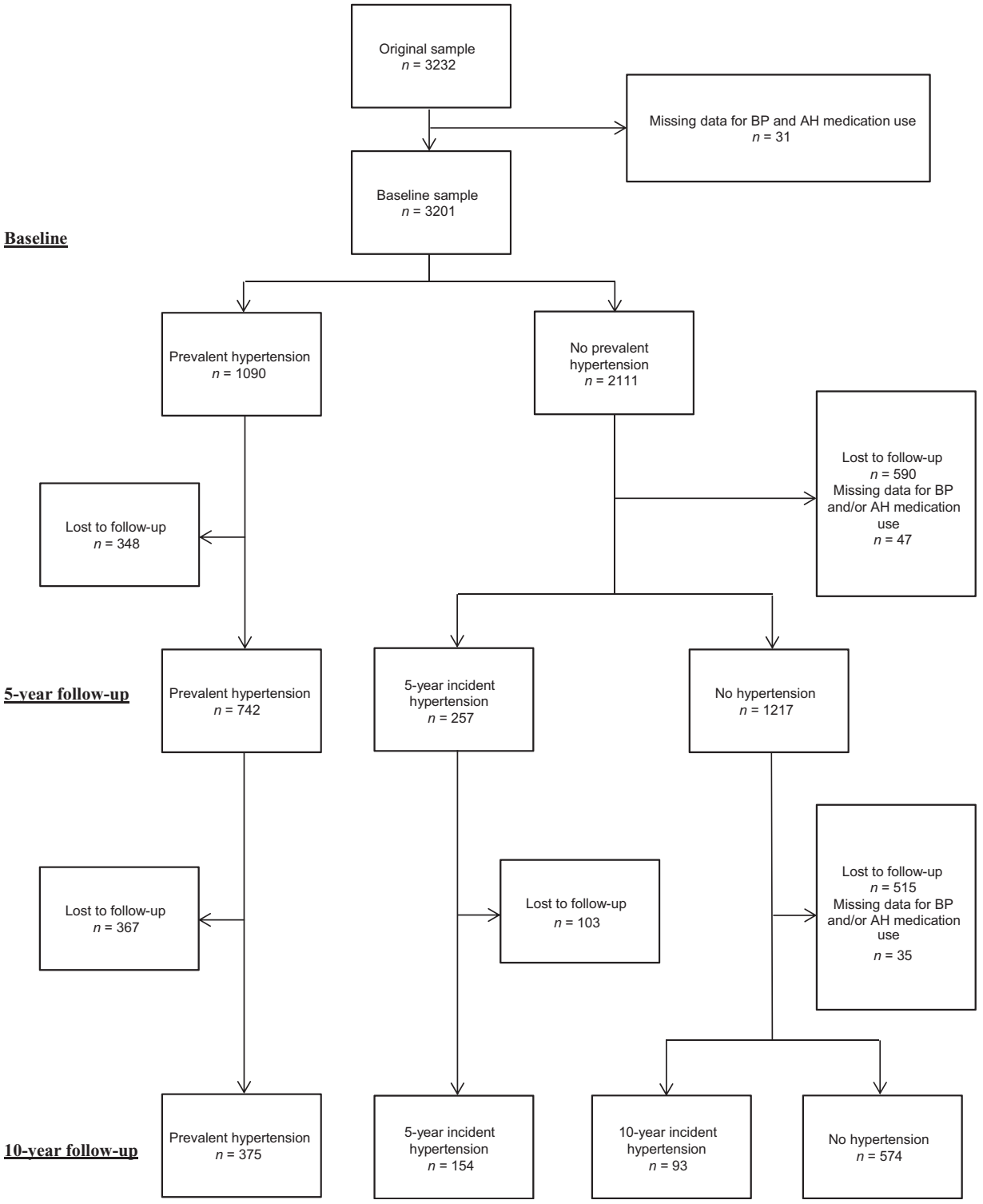

FIGURE 1 Study flow chart. AH, antihypertensive; BP, blood pressure.

especially BP control status at baseline are presented in Table 1. Individuals with incident hypertension had significantly baseline higher BP [SBP: 125 ± 8 vs. 120 ± 9 ($P < 0.001$) and DBP: 76 ± 7 vs. 73 ± 8 ($P < 0.001$)] than individuals without incident hypertension.

Prevalent hypertension and cognitive function

Cognitive performances over time of individuals with and without prevalent hypertension are presented in Fig. 2. Parameter estimates are provided in Table 2.

TABLE 1. Baseline characteristics of participants according to prevalent hypertension and blood pressure control status at baseline ($n = 3201$)

Characteristics	Controlled hypertension[a], $n = 83$ (2.6%)	Uncontrolled hypertension[b], $n = 223$ (7%)	Untreated hypertension[c], $n = 784$ (24.4%)	No hypertension[d], $n = 2111$ (66%)	*P* value
SBP (mmHg), mean ± SD	125 ± 7	151 ± 15	145 ± 12	121 ± 9	<0.001[e]
DBP (mmHg), mean ± SD	76 ± 6	90 ± 10	87 ± 9	73 ± 8	<0.001[e]
Age (years), mean ± SD	51.3 ± 9.3	54.3 ± 7.7	48.6 ± 10.1	42.3 ± 9.4	<0.001[e]
Age (years), *n* (%)					<0.001[f]
32	10 (12.1)	4 (1.8)	124 (15.8)	752 (35.6)	
42	9 (10.8)	35 (15.6)	205 (26.2)	714 (33.8)	
52	41 (49.4)	90 (40.4)	270 (34.4)	484 (23)	
62	23 (27.7)	94 (42.2)	185 (23.6)	161 (7.6)	
Female [*n* (%)]	51 (61.5)	83 (37.2)	233 (29.7)	1192 (56.5)	<0.001[f]
University [*n* (%)]	31 (37.8)	37 (16.6)	157 (20.1)	698 (33.1)	<0.001[f]
Sedentary behavior [*n* (%)]	40 (48.8)	112 (50.9)	389 (49.7)	962 (45.6)	0.14[f]
Active smoking [*n* (%)]	21 (25.3)	47 (21.1)	251 (32.0)	687 (32.5)	0.003[f]
Diabetes mellitus [*n* (%)]	7 (8.4)	32 (14.4)	20 (2.6)	26 (1.2)	<0.001[g]
Dyslipidemia [*n* (%)]	14 (16.9)	72 (32.3)	149 (19)	241 (11.4)	<0.001[f]
Obesity [*n* (%)]	18 (22.0)	60 (26.9)	126 (16.1)	104 (4.9)	<0.001[f]
Cardiovascular diseases [*n* (%)]	3 (3.6)	8 (3.6)	10 (1.3)	14 (0.7)	<0.001[g]
Daily alcohol consumption [*n* (%)]	17 (20.5)	94 (42.2)	323 (41.2)	473 (22.4)	<0.001[f]
High social activities level [*n* (%)]	30 (36.1)	74 (33.2)	284 (36.3)	691 (32.8)	0.32[f]

[a]Controlled hypertension (normal BP with medication use).
[b]Uncontrolled hypertension (high BP despite medication use).
[c]Untreated hypertension (high BP without medication use).
[d]No hypertension (normal BP without medication use).
[e]Kruskall–Wallis test.
[f]Chi-square test.
[g]Fisher's exact test.

Age-stratified analyses were performed (prevalent hypertension × age interaction: $P = 0.03$). In the first 5 years, all participants aged 32 or 42 years old at baseline improved their global cognitive performances. In the second time period, unlike nonhypertensive participants, hypertensive patients showed a declining trend in global cognitive performances. Thus, even in the younger population, hypertensive patients exhibited poorer global cognitive performances at 5-year follow-up and even more at 10-year follow-up ($\beta = -2.99 \pm 0.96$, $P = 0.002$).

When considering participants aged 52 or 62 years at baseline, no improvement in global cognitive performances was found for hypertensive patients in the first period of follow-up whereas a significant decline was reported in the second period of time. Compared with nonhypertensive individuals, hypertensive patients had significant poorer global cognitive performances at each measurement occasion, particularly at 5 and 10-year follow-up ($\beta = -5.94 \pm 1.00$, $P < 0.001$) with a larger gap in comparison with younger individuals.

The examination of memory performances over time revealed somewhat similar results. However, the effect of prevalent hypertension on speed performances was slightly different.

Hypertensive patients aged 32 or 42 years old at baseline had no significant improvement in speed performances over the 10-year follow-up ($\beta = 1.05 \pm 0.62$, $P = 0.09$) in comparison with memory performances ($\beta = 3.49 \pm 0.83$, $P < 0.001$). Older hypertensive patients showed a significant decline in speed performances in the first 5 years. They also exhibited a greater decline over the 10-year follow-up ($\beta = -3.63 \pm 0.62$, $P < 0.001$) compared with memory performances ($\beta = -1.78 \pm 0.67$, $P = 0.008$).

Global cognitive performances over time of individuals according to BP control status for prevalent hypertension are presented in Fig. 3. Parameter estimates are provided in Table 2.

At 5-year follow-up and even more at 10-year follow-up, individuals having the best global cognitive performances were the nonhypertensive ones, followed by controlled hypertensive patients, then by untreated hypertensive patients ($\beta = -5.51 \pm 0.75$, $P < 0.001$) compared with nonhypertensive ones) and finally by uncontrolled hypertensive patients ($\beta = -6.13 \pm 1.40$, $P < 0.001$ compared with nonhypertensive ones).

Incident hypertension and cognitive function

Global cognitive performances over time of individuals with and without incident hypertension are presented in Fig. 4. Parameter estimates are provided in Table 2.

Interestingly, patients with incident hypertension also exhibited poorer global cognitive performances over time compared with patients without hypertension, especially at 10-year follow-up ($\beta = -2.67 \pm 0.85$, $P = 0.002$). Age-stratified analyses (incident hypertension × age interaction: $P = 0.11$) reported that the negative effect of incident hypertension was also true even in the younger population (patients aged 32 or 42 years old at baseline: incident hypertension: $\beta = -3.12 \pm 1.11$, $P = 0.005$ compared with no hypertension at 10-year follow-up).

Finally, we focused on testing the potential effect of attrition (see online-only data supplement, http://links.lww.com/HJH/B44). Out of the 3201 participants included in our study, 29.3% could not be seen again at t2 and 59.5% at t3.

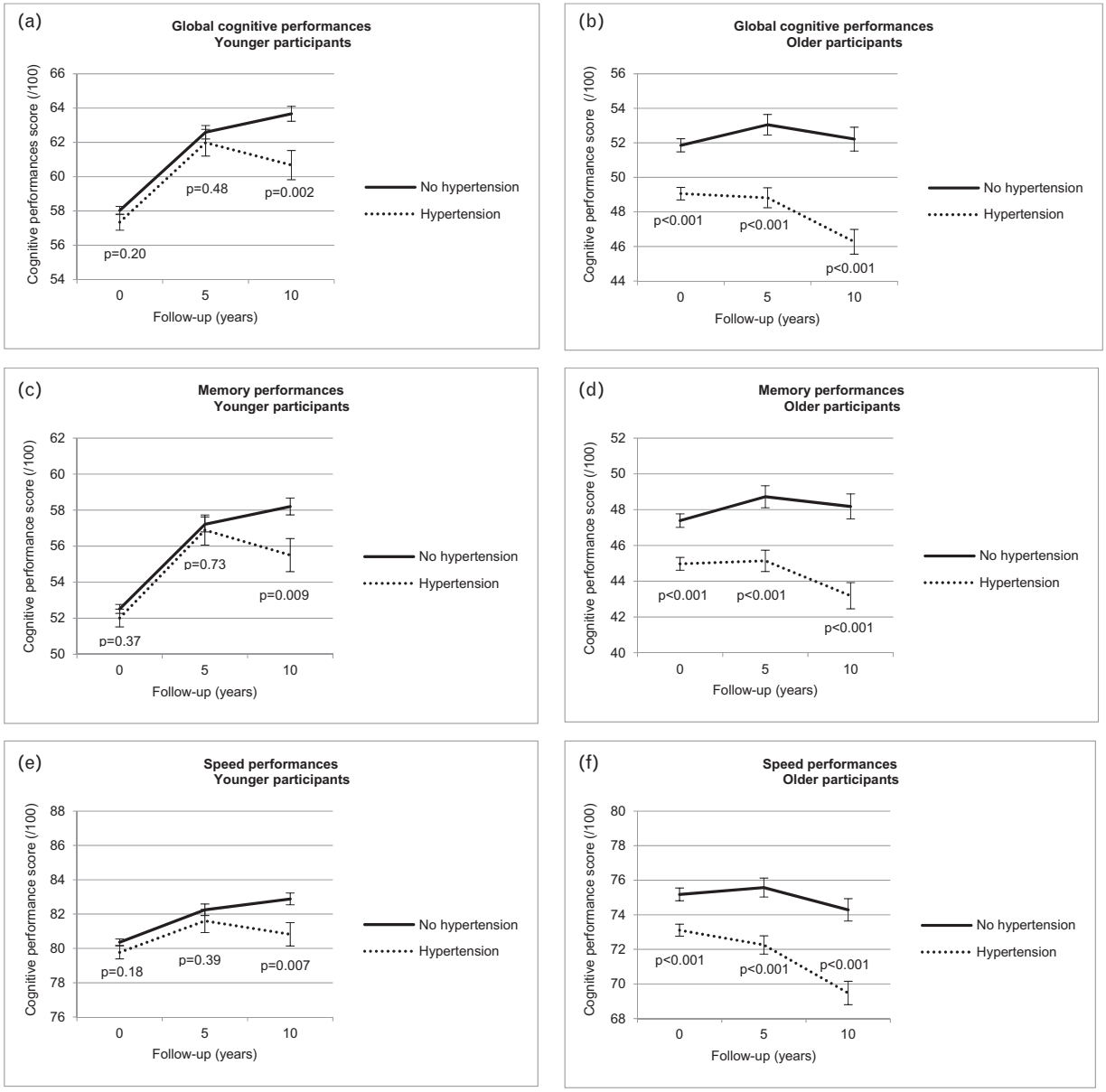

FIGURE 2 Cognitive performances over time of individuals with and without prevalent hypertension, (a) global cognitive performances of younger participants (aged 32 and 42 years at baseline): based on the five cognitive tests (immediate free recall, delayed free recall, delayed recognition measure, digit symbol substitution subtest and selective attention test), (b) global cognitive performances of older participants (aged 52 and 62 years at baseline), (c) memory performances of younger participants: based on the immediate free recall, the delayed free recall and the delayed recognition measure, (d) memory performances of older participants, (e) speed performances of younger participants: based on the digit symbol substitution subtest and the selective attention test, (f) speed performances of older participants, mean (SE) scores of cognitive performances are presented with *P* values indicating differences between groups at each measurement occasion. SE, standard error.

DISCUSSION

Overall, we found that prevalent hypertension was associated with poorer global cognitive performances, not only in older patients but also in participants aged 32 or 42 years at baseline, although to a lesser extent. Interestingly, patients with incident hypertension had also poorer global cognitive performances over time compared with patients without hypertension. This effect was also true for younger patients. Thus, a relatively short exposition to hypertension in younger middle-aged patients was already associated with poorer midlife cognitive function. Moreover, the negative effect of hypertension on cognitive function built up with increasing exposure time and was predominant for information processing speed. Cognitive performances over time also differed according to BP control status, with untreated and uncontrolled hypertensive patients having poorer cognitive performances compared with nonhypertensive individuals.

Overall, our results are consistent with previous findings [3–8,20]. Two recent longitudinal studies provided further evidence to support the association between midlife hypertension and cognitive change [9,10]. In particular, the Atherosclerosis Risk in Communities (ARIC) study reported an amount of decline in the global cognitive *z* score during 20 years for individuals with hypertension 6.5% greater than in

TABLE 2. Parameter estimates about the effect of hypertension and blood pressure control status on global cognitive performance

Model 1a. Effect of prevalent HTN on global cognitive performance in younger participants ($n = 1853$), $\beta \pm$ SE (*P*)				
Differences between groups	-	Baseline	5-year follow-up	10-year follow-up
HTN–non-HTN	-	−0.68 ± 0.53 (0.20)	−0.61 ± 0.88 (0.48)	−2.99 ± 0.96 (0.002)
Differences over time	-	Baseline to 5-year	5-year to 10-year	Baseline to 10-year
non-HTN	-	4.56 ± 0.33 (<0.001)	1.07 ± 0.49 (0.03)	5.64 ± 0.39 (<0.001)
HTN	-	4.63 ± 0.67 (<0.001)	−1.30 ± 0.97 (0.18)	3.33 ± 0.75 (<0.001)
Model 1b. Effect of prevalent HTN on global cognitive performance in older participants ($n = 1348$), $\beta \pm$ SE (*P*)				
Differences between groups	-	Baseline	5-year follow-up	10-year follow-up
HTN–non-HTN	-	−2.79 ± 0.53 (<0.001)	−4.23 ± 0.84 (<0.001)	−5.94 ± 1.00 (<0.001)
Differences over time	-	Baseline to 5-year	5–10 year follow-up	Baseline to 10-year
non-HTN	-	1.19 ± 0.49 (0.02)	−0.83 ± 0.75 (0.27)	0.36 ± 0.60 (0.55)
HTN	-	−0.24 ± 0.47 (0.62)	−2.55 ± 0.77 (<0.001)	−2.79 ± 0.64 (<0.001)
Model 2. Effect of BP control status for prevalent HTN on global cognitive performance ($n = 3201$), $\beta \pm$ SE (*P*)				
Differences between groups	-	Baseline	5-year follow-up	10-year follow-up
Global *P*	-	0.003	<0.001	<0.001
controlled HTN–non-HTN	-	0.30 ± 1.05 (0.78)	−1.64 ± 1.71 (0.48)	−3.50 ± 2.20 (0.45)
Uncontrolled HTN–non-HTN	-	−2.07 ± 0.69 (0.02)	−5.20 ± 1.08 (<0.001)	−6.13 ± 1.40 (<0.001)
Untreated HTN–non-HTN	-	−1.13 ± 0.41 (0.03)	−2.88 ± 0.65 (<0.001)	−5.51 ± 0.75 (<0.001)
Untreated HTN–controlled HTN	-	−1.42 ± 1.08 (0.37)	−1.24 ± 1.76 (0.48)	−2.01 ± 2.54 (0.67)
Untreated HTN– uncontrolled HTN	-	0.94 ± 0.71 (0.37)	2.32 ± 1.14 (0.17)	0.62 ± 1.47 (0.67)
Uncontrolled HTN–controlled HTN	-	−2.37 ± 1.19 (0.19)	−3.56 ± 1.95 (0.20)	−2.63 ± 2.53 (0.67)
Differences over time	Global *P*	Baseline to 5-year follow-up	5-year to 10-year follow-up	Baseline to10-year follow-up
Non-HTN	<0.001	3.54 ± 0.28 (<0.001)	0.69 ± 0.42 (0.10)	4.24 ± 0.33 (<0.001)
Controlled HTN	0.53	1.61 ± 1.43	−1.17 ± 2.36	0.43 ± 1.99
Uncontrolled HTN	0.88	0.42 ± 0.85	−0.24 ± 1.43	0.18 ± 1.22
Untreated HTN	<0.001	1.79 ± 0.46 (<0.001)	−1.94 ± 0.71 (0.01)	−0.15 ± 0.57 (0.80)
Model 3. Effect of incident HTN on global cognitive performance ($n = 2111$), $\beta \pm$ SE (*P*)				
Differences between groups	-	Baseline	5-year follow-up	10-year follow-up
HTN–non-HTN	-	−0.18 ± 0.54 (0.74)	−1.48 ± 0.79 (0.06)	−2.67 ± 0.85 (0.002)
Differences over time	-	Baseline to 5-year follow-up	5-year to 10-year follow-up	Baseline to 10-year follow-up
Non-HTN	-	3.86 ± 0.31 (<0.001)	1.09 ± 0.47 (0.02)	4.95 ± 0.38 (<0.001)
HTN	-	2.56 ± 0.57 (<0.001)	−0.10 ± 0.80 (0.90)	2.46 ± 0.62 (<0.001)

Controlled hypertension (normal BP with medication use); uncontrolled hypertension (high BP despite medication use); untreated hypertension (high BP without medication use); nonhypertension (normal BP without medication use). Linear mixed models 1: prevalent hypertension, measurement occasion, prevalent hypertension × measurement occasion, age (stratification), sex, educational level, sedentary behavior, active smoking, type 1 or 2 diabetes, dyslipidemia, obesity, cardiovascular diseases (myocardial infarction, angina pectoris, stroke), daily alcohol consumption. Linear mixed models 2: BP control status, measurement occasion, BP control status × measurement occasion, age, sex, educational level, sedentary behavior, active smoking, type 1 or 2 diabetes, dyslipidemia, obesity, cardiovascular diseases (myocardial infarction, angina pectoris, stroke), daily alcohol consumption. Linear mixed models 3: incident hypertension, measurement occasion, incident hypertension × measurement occasion, age, sex, educational level, sedentary behavior, active smoking, type 1 or 2 diabetes, dyslipidemia, obesity, cardiovascular diseases (myocardial infarction, angina pectoris, stroke), daily alcohol consumption. BP, blood pressure; HTN, hypertension; *P*, *P*-value.

individuals with normal BP. However, very few studies investigated the relationship between incident hypertension and cognitive changes over time. Our findings are consistent with the MAAS study [21], which reported poorer cognition function in incident hypertensive participants. Yet, our multicenter cohort study, conducted in a two-fold larger sample of patients, adds that the negative effect of incident hypertension on cognitive performances is also true for even younger middle-aged individuals.

Our results indicated that participants tended to improve their cognitive performances in the first period of follow-up. This improvement, statistically but not clinically significant, could be related to tests familiarization over time [22]. The effect of hypertension in the first period of time consisted in a reduced improvement of cognitive performances whereas it led to a cognitive decline in the second period of time, suggesting a dose–response relationship.

Evidence has emerged that long-term hypertension increases arterial stiffness, leading to severe cerebral atherosclerosis and ischemic conditions [3,23–25]. However, the effects of elevated high BP have already been demonstrated as early as the fifth decade of life [26]. These findings are consistent with our results in which hypertension was found to have negative effects on middle-aged cognition.

Interestingly, compared with nonhypertensive participants, hypertensive patients exhibited worse performances in information processing speed. Similar trend has already been reported in previous studies [27], particularly in the Framingham Third Generation Cohort study [28], in which higher aortic stiffness was associated with poorer processing speed performances in middle-aged adults.

Finally, our results indicated that cognitive performances over time differed according to BP control status. Our findings showed, although the results did not reach statistical significance, that successful hypertension treatment did not totally reverse cognitive impairment associated with hypertension. Similar results have been previously found regarding cognitive function as well as cardiovascular diseases with the PRIME study [29] suggesting the existence of a residual cardiovascular risk. First, such a residual risk regarding cognitive function could be related to a late onset of antihypertensive treatment leading to irreversible brain damages. Second, despite normal mean blood pressure levels, potential higher blood pressure variability in treated hypertensive patients could partly explain such a residual risk [30]. Third, an increased risk of cognitive impairment in treated hypertensive patients could be partly attributable to a greater subclinical disease burden. Our results also showed that both uncontrolled and untreated hypertensive

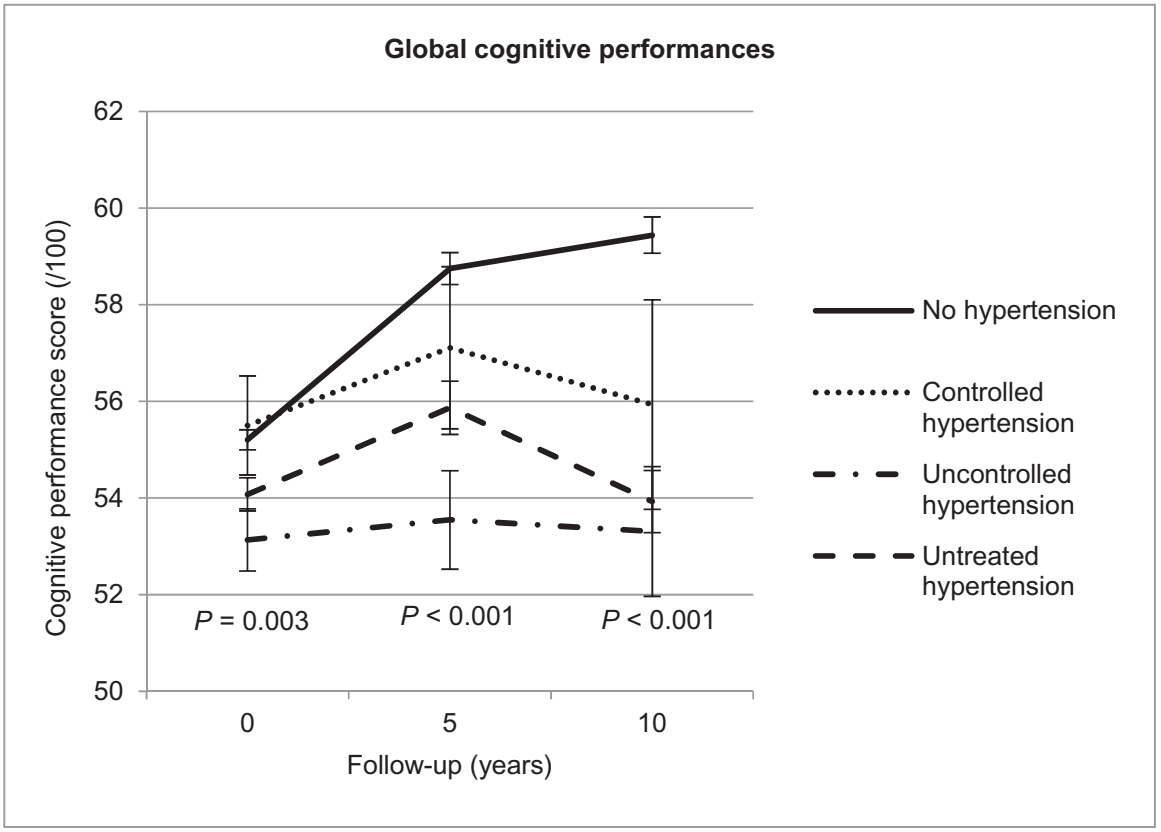

FIGURE 3 Global cognitive performances over time of individuals according to blood pressure control status for prevalent hypertension, controlled hypertension [normal blood pressure (BP) with medication use]; uncontrolled hypertension (high BP despite medication use); untreated hypertension (high BP without medication use); no hypertension (normal BP without medication use), mean (SE) scores of cognitive performances are presented with *P* values indicating global differences between groups at each measurement occasion. SE, standard error.

patients had significant poorer cognitive performances compared with nonhypertensive participants. Similar trend was found in comparison with controlled hypertensive patients even if, because of a small subgroup and a lack of statistical power, the results were not significant. These results are supported by previous studies [20,31], particularly data indicating that untreated and poorly controlled hypertension are associated with a decline in cerebral flood flow [32,33] and greater white matter lesions volume [34]. Surprisingly, untreated hypertensive patients exhibited better cognitive performances than uncontrolled hypertensive participants, although the difference did not reach significance. Yet, accumulating evidence has emerged that antihypertensive therapy could decrease the incidence and progression of cognitive impairment and cognitive decline, not only by lowering BP but also through a neuroprotective specific effect [35]. Thus, untreated hypertensive patients were expected to have lower cognitive performances than uncontrolled hypertensive participants. However, uncontrolled hypertensive patients had on average higher BP levels and more cardiovascular comorbidities. Overall, our results indicated that for brain functioning, heightened efforts to detect hypertension and adequately treat it are of critical importance. This is consistent with the recent work conducted in the Framingham Heart study [36], which found that the decreasing incidence of dementia observed over three decades could be partly explained by a better control of vascular risk factors, including hypertension.

Our study suffers from several limitations. Sample attrition during the course of the study is one of them. In our working population, the main reasons for loss to follow-up were retirement and change of company's occupational physician. However, the proportion of patients lost to follow-up in the VISAT study is similar to other cohorts of workers, particularly the ESTEV study [37]. Attrition was not likely to be related with potential cognitive decline. Although attrition bias cannot be fully ruled out, it may not have biased our conclusions. Indeed, the fact that the proportion of patients lost to follow-up was higher in the prevalent hypertension group and that these patients had baseline lower cognitive performances compared with nonhypertensive individuals lost to follow-up may have rather led to an underestimation of the potential negative effect of hypertension on cognitive performances. Moreover, sensitivity analyses conducted under the assumption that participants could be lost to follow-up because of greater decline in cognitive performances over time showed that our results were robust.

Another weakness of our study is the lack of statistical power in some respects. Despite a large number of participants, some subgroups were small, particularly the controlled and uncontrolled hypertension groups, sometimes leading to fewer possibilities to find significant differences.

Data regarding dietary pattern were not available. Various epidemiological studies suggested that, for the most part, nutrients that increase risk for cardiovascular diseases,

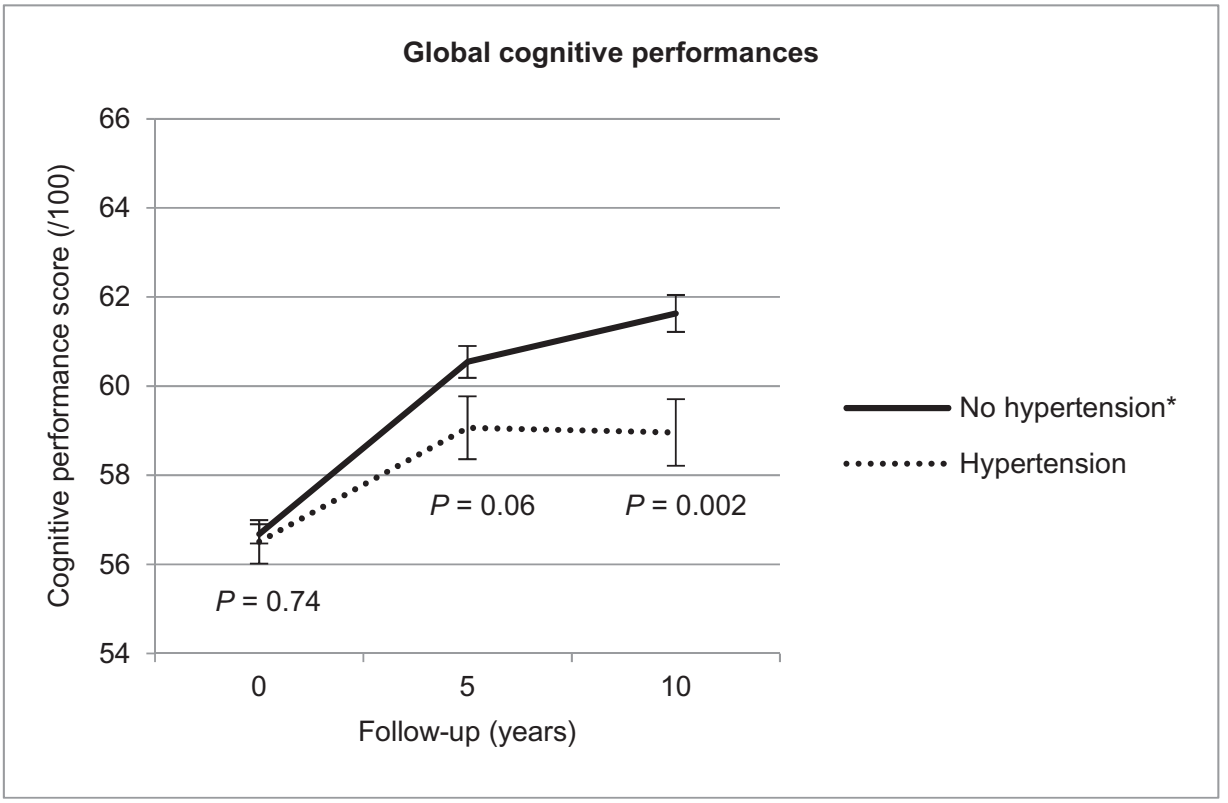

FIGURE 4 Global cognitive performances over time of individuals with and without incident hypertension, global cognitive performances (younger and older participants): based on the five cognitive tests (immediate free recall, delayed free recall, delayed recognition measure, digit symbol substitution subtest and selective attention test), mean (SE) scores of cognitive performances are presented with *P* values indicating differences between groups at each measurement occasion. SE, standard error.

such as trans-fats and added sugars, would also increase risk for cognitive decline and dementia, at least in part through vascular damage in the brain [38]. Conversely, multinutrient approaches such as the Mediterranean diet may have potential benefits [39]. Thus, residual and unmeasured confounding regarding dietary factors could not totally be excluded in our study. However, in their work aiming to determine whether there was an interaction between hypertension and dietary pattern in relation to older people's cognition, Xu *et al.* [40] did not find such interaction but found hypertension to be an independent risk factor for cognitive functioning even after adjustment for dietary pattern. Finally, thus far, hypertension is recognized as the strongest and the most consistent modifiable risk factor for cognitive impairment and dementia whereas dietary pattern still needs further validation [41,42].

Misclassification of exposure may have been a limitation. BP measurement was only done in the office, without ambulatory monitoring, potentially leading to a white coat effect.

Antihypertensive therapy was self-reported and we cannot totally exclude the possibility of a recall bias. Antihypertensive drug classes were not collected at baseline. Patients were only asked if they were currently treated by antihypertensive drugs. Thus, the impact of specific antihypertensive drug consumption on temporal evolution of cognitive changes over the 10-year follow-up could not be assessed. Duration of antihypertensive therapy was unknown, particularly regarding prevalent hypertension. Patient compliance was not assessed in our study.

No information was available regarding the age of onset of hypertension. However, we focused on testing the potential impact of both prevalent and incident hypertension on cognitive performances over time. In both cases, hypertension had a negative impact even in younger individuals, probably diagnosed as quite recent hypertensive patients because of their age. Under the assumption that the effect of hypertension on cognitive performances builds up with increasing exposure time, if patients had been diagnosed as hypertensive patients longer before entering the study, they would have exhibited even worse cognitive performances. Moreover, assessing the accurate onset of such a chronic disease as hypertension might sometimes be quite difficult.

Despite these limitations, our study has notable strengths. First, it was conducted in a large sample of middle-aged adults with a period of follow-up long enough to identify cognitive changes over time while still allowing to explore the effect of hypertension on midlife cognitive function. Second, we addressed the potential benefits of BP control by antihypertensive therapy. Moreover, the effect of

both prevalent and incident hypertension was investigated. Third, memory and speed-based tests were administered, providing particular opportunity to create composite measures of cognitive performances.

In conclusion, our results indicated that both prevalent and incident hypertension in middle-aged adults were associated with poorer midlife cognitive performances, especially regarding information processing speed. Our findings also reported that the negative effect of hypertension on cognitive function builds up with increasing exposure time. When considering BP control status by antihypertensive therapy, untreated and uncontrolled hypertension were significantly associated with poorer cognitive performances compared with no hypertension. Similar trend was found in comparison with controlled hypertension, suggesting that control of hypertension is of critical importance to prevent cognitive decline.

Perspectives

In summary, our study reported that both prevalent and incident hypertension are associated with poorer global cognitive performances in middle-aged individuals. Very interestingly, the negative effect of hypertension on cognition was already true in younger patients with a short exposition to high blood pressure. Moreover, our findings suggested that control of hypertension is of critical importance to prevent cognitive decline, especially in young newly diagnosed hypertensive patients. This study is of great importance in the preservation of healthy cognitive aging by emphasizing the need for early detection of hypertension and tight control of blood pressure. As suggested by our results, the first objective of treatment should be a blood pressure goal less than 140/90 mmHg in all patients but, provided that the treatment is well tolerated, lower blood pressure thresholds and treatment targets should be considered according to patient's age and specific comorbidities in accordance with the 2018 ESC/ESH Guidelines for the management of arterial hypertension [43]. Finally, our study highlighted the importance in hypertensive patients to pay particular attention to processing speed and executive functions when assessing cognitive performances. The Montreal Cognitive Assessment (MoCA) [44], because of its high sensitivity, should be considered in clinical practice for detecting hypertension-associated cognitive impairment.

ACKNOWLEDGEMENTS

The authors are grateful to the occupational physicians and other researchers of the VISAT group, who contributed to the VISAT program.

Sources of funding: This work was funded by grants from the French Agence Nationale de la Recherche (ANR 2006 SEST 04 101), the Institute of Occupational Safety & Health (IOSH, UK), and the Direction Générale de la Santé (DGS), la Caisse Nationale d'Assurance Maladie des Travailleurs Salariés (CNAMTS), du Régime Social des Indépendants (RSI) et de la Caisse Nationale de Solidarité pour l'Autonomie (CNSA), as part of the call for projects launched by Institut de Recherche en Santé Publique (IReSP) in 2009. All authors were independent from the funders.

Conflicts of interest

L.R. reports no disclosures; P.C. reports no disclosures; O.H. reports no disclosures; J.-B.R. reports no disclosures; V.E. reports no disclosures; C.G. reports no disclosures; C.C. reports no disclosures; C.H. reports personal fees from Novartis Pharma, outside the submitted work. J.-F.D. reports grants from Ipsen and Roche; B.B. has served as a consultant for Lilly and Astra Zeneca, reports grants from Novartis and Sanofi, outside the submitted work; B.C. reports no disclosures; B.S. reports no disclosures; B.V. has served as a scientific board member for Biogen, GSK, Lilly, Lundbeck, Medivation, MSD, Nestlé, Nutricia, Pfizer, Roche, Sanofi, Servier, TauRx Therapeutics, Alzheon, Transition Therapeutics, Takeda; reports grants from Abbvie, Affiris, Avid, BMS, Eisai, Elan, Envivo, Exhonit, Genentech, GSK, Ipsen, Lilly, Lundbeck, Medivation, MSD, Nutricia, Otsuka, Pharnext, Pfizer, Pierre-Fabre, Regeneron, Roche, Sanofi, Servier, TauRx Therapeutics, Wyeth, Astra-Zeneca, LPG Systems. J.-C.M. reports no disclosures; Y.E. reports no disclosures; S.A. reports grants from EU-JPND program, EU-FP7 program, Beaufour Ipsen Pharma, France Alzheimer Association ; personal fees from Beaufour Ipsen Pharma, Pierre Fabre, Lilly, Nestlé, Sanofi, Servier; nonfinancial support from Biogen, Nutrition Santé, Pfizer, Icon, AMPA Association; outside the submitted work.

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