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Hypertension and Lower Walking Speed in the Elderly: the Three-City Study

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There are no conflicts of interest.

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Objective The brain is one of the main targets of hypertension. However, little is known about the relation between hypertension and motor performances. We studied the association between hypertension and walking speed in a cohort of elderly people.

Methods Analyses are based on participants (65-85 years) from the Dijon (France) center of the Three-City study (n=3604), followed every two years. Persistent hypertension was defined by the use of antihypertensive drugs at baseline or at first follow-up, or by high blood pressure (≥140/90 mmHg) at baseline and first follow-up. Walking speed was measured over 6 meters, at baseline and fourth follow-up (n=1774) after a mean (SD) duration of 7.0 (0.5) years. Brain MRI was performed in 1590 participants. Generalized linear models were used to assess the relation between hypertension and baseline walking speed or walking speed change.

Results At baseline, mean (SD) walking speed (m/s) was lower in hypertensive subjects (1.51 [0.31]) than in non-hypertensive subjects (1.59 [0.30], P<0.001). During follow-up, hypertensive subjects had a higher mean annual decline in walking speed (cm/s per year; 2.30 [3.4]) than non hypertensive subjects (1.87 [3.3], P=0.004). The number of antihypertensive drugs was associated with lower walking speed at baseline and higher walking speed decline. Adjustment for MRI white matter abnormalities attenuated these relations.

Conclusion Persistent hypertension was associated with both lower walking speed and higher decline in walking speed in the elderly. These results may be partly explained by white matter abnormalities, and support the hypothesis of a contribution of vascular risk factors to motor dysfunction.

Condensed abstract

Little is known about the relationship between hypertension and motor performances in the elderly. We studied the association between hypertension and walking speed in a large cohort of well-functioning French elderly subjects (n=3604). Hypertensive subjects had a lower walking speed at baseline, and a higher decline of walking speed over a mean follow-up of 7 years. These results may be partly explained by white matter abnormalities, and support the hypothesis of a contribution of vascular risk factors to motor dysfunction in the elderly.

Key words: hypertension, gait, aging, epidemiology, cerebrovascular disorders

Abbreviations: 3C, Three-City Study; BMI, body mass index; BP, blood pressure; MMSE, Mini-Mental State Examination; NSAID, non-steroidal anti-inflammatory drug; WMH, white matter hypersignal

Introduction

The etiology of gait disorders and decreased motor performances in the elderly is likely to be multifactorial [1], and recent evidence points to the role of vascular risk factors such as diabetes mellitus [2], increased homocysteine [3], or low HDL cholesterol [4]. Hypertension is highly prevalent among the elderly [5], and is a major risk factor for cerebrovascular disease, including clinical stroke and subclinical cerebral white matter lesions [6]. While some studies have shown that hypertension is a risk factor for cognitive decline and dementia [7, 8], little is known about its relation with motor function in the elderly.

Walking speed is a simple and reliable measure that is considered as a surrogate for overall quality of gait and motor function [9], and provides similar information as does a more comprehensive summary measure of physical performance [10]. Decreased walking speed has been shown to be strongly associated with adverse health-related events such as falls [11], disability [12], hospitalization [13], and death [10].

The aim of this study was therefore to investigate the cross-sectional and longitudinal association between hypertension and walking speed in a sample of community-dwelling nondisabled elderly subjects, as part of the Three-City (3C) study.

Methods

Study Population

The 3C study is a prospective cohort of community-dwelling persons aged 65 years and over living in three French cities (Bordeaux, Dijon, and Montpellier). The study design has been described elsewhere [14]. A specific sub-study on motor function was performed in Dijon (N=4399) where walking speed was measured at baseline

(1999-2000) in subjects aged 85 years old or younger. At baseline, 3604 participants were included for cross-sectional analyses, after exclusion of those with conditions that strongly affected motor function (dementia, disabling stroke, hip fracture, Parkinson's disease). Following the baseline examination, participants were seen at 4 follow-up surveys. The first, second, and fourth follow-up examinations took place over periods of 2 years. They consisted in at home interviews followed by an examination at the study center. The third follow-up consisted in self-administered questionnaire mailed at home, and data collection took place during one year. After the baseline measure of walking speed, it was measured again at the fourth follow-up, after a mean (SD) duration of 7.0 (0.5) years. A total of 1774 subjects were included for longitudinal analyses, after exclusion of subjects with incident diseases affecting motor function (dementia, disabling stroke, hip fracture, Parkinson's disease) and those with missing values for a walking speed measure at the fourth follow-up. The flow-chart of participants enrolled in the analyses is presented in Figure 1.

The study protocol was approved by the Ethical Committee of the University- Hospital of Bicêtre (France) and written informed consent was obtained from each participant.

Data Collection

Baseline demographic and medical data were collected at home during face-to-face interviews using a standardized questionnaire administered by trained psychologists. Education level was defined as no school or primary without diploma, primary with diploma, secondary without a baccalaureate degree, baccalaureate or university degree. Weight and height were measured and used to calculate body mass index (BMI). Physical activity level was defined based on the daily duration of walking and

athletic activities; low physical activity level was considered for subjects who answered “very little or none” for the daily duration of walking and had no athletic activity. The interview also included an inventory of all drugs prescribed during the preceding month. The name of the medication was recorded, and all drugs were subsequently coded according to the French translation of the WHO ATC classification [15]. Chronic consumption of non-steroidal anti-inflammatory drugs (NSAIDs) for joint pain was assessed and used as surrogate for rheumatic disease. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D) [16]. Global cognitive function was assessed by the Mini-Mental State Examination (MMSE) [17]. Subjects were considered as diabetic if they used antidiabetic agents or if their fasting glucose level was equal to or greater than 7.0 mmol/L. Hypercholesterolemia was defined as total cholesterol ≥ 7.25 mmol/L or by use of lipid-lowering drugs. Smoking status was classified as current, past, or never. History of coronary heart disease and peripheral artery disease was assessed by questionnaire. Exertional dyspnea was self-declared using the New York Heart Association classification [18].

Definition of Hypertension

At each examination, blood pressure (BP) was measured twice at home by the interviewers after at least 5 minutes of rest in a seated position, with an appropriately sized cuff placed on the right arm and using a validated digital electronic tensiometer (OMRON M4). The mean of both measures was used in the analyses. Use of antihypertensive drugs was determined according to the number and the type of antihypertensive drugs taken to lower blood pressure: diuretics, beta-blockers, angiotensin converting enzyme inhibitors, calcium channel blockers, and others (ATC code C02).

Participants were considered as having persistent hypertension if they were treated by antihypertensive drugs for hypertension at baseline or at first follow-up, or if they had high blood pressure (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg) at baseline and at first follow-up. This definition of persistent hypertension was therefore based on two measures taken at two different time-points (baseline and first follow-up examinations; mean [SD] delay between the two measures = 1.8 [0.17] years) in order to reduce the risk of misclassifying hypertensive status [19, 20].

Walking Speed Assessment

At baseline, following the home interview, participants aged 85 years old or younger were invited to the study center where walking speed was measured. Two photoelectric cells connected to a chronometer were placed in a corridor 6 meters apart. Participants were asked to walk in the corridor at their maximum speed. The time needed to cover 6 meters was measured by the photoelectric cells, and walking speed was computed as 6 meters divided by time in seconds.

To assess the reproducibility of this measure, we performed a test-retest study in 51 subjects (mean [SD] age = 71.1[3.4] years). Two measures of maximum walking speed were taken five minutes apart. The intraclass correlation coefficient (SE) was 0.92 (0.02), thus showing high reproducibility, as in previous studies.[21]

Walking speed was measured again using the same protocol at the fourth follow-up, in subjects aged 85 years old or younger at that time who agreed to come to the study center. Annual walking speed change (in centimeters per second per year) was

defined as the baseline walking speed measurement minus the follow-up walking speed measurement, divided by the duration between the two measurements.

Brain MRI

Brain MRI was proposed to all participants aged ≤ 80 years enrolled between June 1999 and September 2000 (N=2673); 2285 subjects (82%) accepted but only 1924 scans were performed because of financial limitations. Exclusion criteria for MRI were cardiac pace-maker, valvular prosthesis, or other internal electrical/magnetic devices; history of neurosurgery/aneurysm; claustrophobia; and presence of metal fragments. The detailed MRI protocol has been previously described [22, 23]. MRI acquisition was performed on a 1.5T Magnetom (Siemens, Erlangen, Germany). Fully automated image processing software was developed to measure white matter lesions (WML) volume [23]. The presence of lacunar infarcts was assessed visually by a neurologist using a standardized assessment grid.

Statistical Analysis

Baseline characteristics of the study population are presented overall and according to tertiles of walking speed and to hypertensive status, and were compared using the chi-square statistic for categorical variables or the Student t-test for continuous variables.

Generalized linear models were used to study the relation between walking speed (considered as the dependent variable) and hypertensive status. In a first model, in addition to hypertension, three covariates strongly associated with walking speed and hypertension (age, sex, BMI) were included. In a second model, we included additional covariates associated both with walking speed and hypertension in

univariate analyses (education level, MMSE, physical activity, hypercholesterolemia, smoking, NSAIDs use). In a third model, we included variables associated with either hypertension or walking speed. In a fourth and final model, we adjusted for potential mediators: history of coronary heart disease or peripheral artery disease, and exertional dyspnea.

For longitudinal analyses, the characteristics of the study sample are presented overall and according to tertiles of annual walking speed change, and were compared using the chi-square statistic for categorical variables or the Student t-test for continuous variables. Generalized linear models were used to study the relation between annual walking speed decline (considered as the dependent variable) and hypertension. In a first model, in addition to hypertension, age, sex, baseline walking speed, and BMI were included. In a second model, we included additional covariates associated both with walking speed decline and hypertension (education level, hypercholesterolemia, smoking, physical activity level, diabetes mellitus, psychotropic drug use). In a final model, we included history of coronary heart disease and peripheral artery disease, as well as exertional dyspnea as covariates.

We studied the relation between the number of different antihypertensive drugs used at the same time and baseline walking speed or annual walking speed decline; we considered that a higher number of antihypertensive drugs represents a surrogate marker for the severity of hypertension [24, 25].

Because of a large difference in walking speed in men and women, all analyses were systematically stratified by sex.

To investigate differences in walking speed across the main categories of antihypertensive drugs, we restricted the analyses to subjects treated for hypertension with a monotherapy and we defined the following 4-level categorical variable: users of diuretics, beta-blockers, angiotensin converting enzyme inhibitors, calcium channel blockers; mean walking speed was compared across the levels of this variable using the Tukey-Kramer method to adjust for multiple comparisons.

We performed sensitivity analyses. As beta-blockers can induce fatigue or dyspnea during physical exercise [26], we excluded participants using beta-blockers, to investigate whether the relations observed were explained by this category of drugs. We also used multiple imputation procedures to impute missing values of walking speed at the fourth follow-up using a general linear regression model (10 imputations) including baseline predictors (age, gender, BMI, walking speed, hypertensive status) and the delay between baseline and follow-up examinations (SAS Proc MI). Imputed data sets were analyzed as complete data and the 10 sets of results were pooled using SAS Proc MIANALYZE.

Finally, to investigate whether MRI abnormalities related to hypertension (WML volume, lacunar infarcts) explained the association between hypertension and walking speed, we repeated our cross-sectional and longitudinal analyses among subjects who performed a brain MRI at baseline. In a first model we adjusted for age, sex, and BMI. In a second model, we added WML volume and presence of lacunar infarcts.

All *P* values were two-tailed; $P \leq 0.05$ was considered to be statistically significant. Statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics of the study population (N=3604) are presented in Table 1. The mean (SD) age of the participants was 73.4 (4.6) years, 61.9% of them were women, and 71.4% had persistent hypertension. Subjects who walked slower were older, heavier, more often women, and were more likely to have depressive symptoms and exertional dyspnea than those who walked faster. They also had a lower educational, MMSE, and physical activity level, were more often treated for hypercholesterolemia, and used more frequently NSAIDs and psychotropic drugs. These associations remained significant after adjustment for age and sex. Subjects who walked faster were more often ever-smokers and current alcohol drinkers than those who walked slower; however, this relation was explained by a strong confounding effect of sex and age, and it was no longer significant after adjustment for these two variables (smoking, p=0.88; alcohol, p=0.14). Hypertension was associated with older age, male sex, higher BMI, lower education, MMSE, and physical activity level, and other vascular risk factors (diabetes, hypercholesterolemia, smoking), exertional dyspnea, and history of coronary and peripheral artery disease (Table 1); these associations remained significant after adjustment for age and sex, except for peripheral artery disease (p=0.11) and smoking (p=0.46).

The cross-sectional relation between hypertension and walking speed at baseline is presented in Table 2. Hypertensive subjects had a lower mean walking speed (1.51

[0.31] m/s) than non-hypertensive subjects (1.59 [0.30]). This difference was significant after adjustment for age, sex, and BMI (model 1, P value <0.001). There was a progressive decrease in mean walking speed with an increasing number of antihypertensive drugs used (p for trend <0.001). Further adjustment for potential confounders (models 2 and 3) or mediators (model 4) yielded similar findings. This relation was present and of the same magnitude in men and women (Table 2). Among subjects treated for hypertension with a monotherapy, there were no significant differences in baseline walking speed across the main types of antihypertensive drugs (p-values ranging from 0.11 to 0.99 after adjustment for age, sex, and BMI).

Among the 2755 subjects eligible for a walking speed assessment at the fourth follow-up, a second measure was not available for 981 subjects (Figure 1). They walked slower and were older, heavier, more often women, and more likely to have hypertension, depressive symptoms, diabetes mellitus, and a low physical activity level at baseline than subjects with a second walking speed measure. Table 3 presents the baseline characteristics of the participants included in longitudinal analyses (N=1774). A higher annual decline in walking speed was associated with older age, male sex, higher BMI, higher baseline walking speed, lower education and physical activity level, smoking, use of psychotropic drugs, diabetes mellitus, coronary disease, and exertional dyspnea.

Analyses of the relation between hypertension and annual walking speed decline are presented in Table 4. After adjustment for baseline walking speed, age, sex, and BMI (model 1), subjects with hypertension had a higher mean annual decline in walking speed (2.30 [3.4] cm/s per year) than non-hypertensive subjects (1.87 [3.3],

p=0.004). An increasing number of antihypertensive drugs was also associated with a higher annual rate of walking speed decline (model 1, p for linear trend <0.001). Further adjustment for potential confounders (model 2) or mediators (model 3) yielded similar results. This association was not modified by gender (interaction p-values ranging from 0.87 to 0.93). Among subjects treated for hypertension with a monotherapy, there were no significant differences in annual decline in walking speed across the main types of antihypertensive drugs (p-values ranging from 0.40 to 0.99 after adjustment for age, sex, BMI, and baseline walking speed).

In sensitivity analyses, we excluded beta-blocker users from the analyses (cross-sectional analysis, N=717; longitudinal analysis, N=300). At baseline, after adjustment for age, sex and BMI, hypertension was still associated with lower walking speed (model 1, β [SE] = -0.033 [0.011], p=0.002). After adjustment for baseline walking speed, age, sex and BMI, hypertension was still associated with a higher annual decline in walking speed (model 1, β [SE] = 0.42 [0.16], p=0.009).

In longitudinal analyses including multiple imputation of missing values of walking speed at the fourth follow-up in 981 participants, we found that, after adjustment for baseline walking speed, age, sex, and BMI, hypertension was still associated with higher annual decline in walking speed (model 1, β [SE] = 0.31 [0.14], p=0.03). Additional adjustment for potential confounders or mediators did not modify these relations (model 3, β [SE] = 0.28 (0.14), p=0.04).

At baseline, a brain MRI was available for 1590 subjects (figure 1). The mean (SD) age of subjects with a MRI was 73.2 (4.1) years, 60.5% of them were women, and 68.2% were hypertensive. The mean (SD) WML volume was 5.5 (5.0) cm^3, and 7.0%

of subjects had at least one lacunar infarct. Table 5 presents the relation between hypertension and walking speed among subjects who performed a brain MRI at baseline. Adjustment for WML volume and the presence of lacunar infarcts attenuated the relation between hypertension and baseline walking speed (decrease in regression coefficient = 16.3%), and walking speed decline (decrease in regression coefficient = 18.4%).

Discussion

In this large prospective cohort of non-institutionalized elderly individuals, hypertension was associated with lower walking speed at baseline and with a higher annual rate of decline in walking speed over follow-up. Using the number of antihypertensive drugs used as a surrogate for the severity of hypertension, we found that these associations were characterized by a dose-effect pattern. These relations were present both in men and women, and remained after adjustment for several potentials confounders and mediators. Adjustment for WML volume and presence of lacunar infarcts at MRI attenuated these relations.

Few studies have investigated the relation between hypertension and motor function in the elderly. In the Women's Health Initiative, hypertensive women aged 50 to 79 years old had a lower walking speed as part of their baseline assessment [27]. In other studies, hypertension was associated with slower long-distance corridor walk [28], and increasing systolic blood pressure was associated with the decline in a composite measure of lower limb function [29]. Hypertension was also found to be associated with direct or indirect markers of physical fitness like activities of daily living [30], frailty [31], or increased time to complete the Up and Go test [32].

To study the relation between motor performances and hypertension, we used a simple and reliable test, i.e. walking speed, that can be assessed with high reliability in many settings. In addition, using the number of drugs used as a surrogate for hypertension severity [24, 25], our findings are suggestive of dose-effect pattern. Finally, we adjusted our analyses for several potential confounders or mediators and found consistent results in cross-sectional and longitudinal analyses.

We defined persistent hypertension based on two measures of blood pressure taken at two different time points in order to reduce the risk of misclassifying hypertensive status. Indeed, the prevalence of high blood pressure (≥140/90 mm Hg) was considerably higher at baseline (67.6%) than at the first (47.6%) or second follow-up (46.4%) exams. An excess of participants with high blood pressure at baseline in cohort studies has already been described [20], and may be partly explained by a white-coat effect. Participants who had high blood pressure at two subsequent time points were more likely to be truly hypertensive; our approach is in agreement with international recommendations requiring two separate measures of elevated blood pressure for the diagnosis of hypertension [33].

Various mechanisms may account for the association between hypertension and lower walking speed. Hypertension is a major risk factor for cerebrovascular disease, including stroke and WML seen on cerebral MRI [6]. Several studies have shown that WML are associated with worse motor performances [34, 35], suggesting perturbations of neural networks due to small vessel pathology [36]. In our analyses, adjustment for white matter abnormalities attenuated the relations between hypertension and baseline walking speed, and walking speed decline. This result

suggests that white matter abnormalities may be an intermediate factor in the relation between hypertension and lower walking speed in the elderly. We therefore hypothesize that the relation between hypertension and walking speed may be, at least partly, explained by the central neurological consequences of hypertension.

Alternative mechanisms may be involved. Hypertension is a major risk factor for atherosclerosis and leads to peripheral artery and coronary disease, which may be responsible for poorer physical performances. However, adjustment for these conditions did not modify the observed relations. A class-effect of antihypertensive drugs is unlikely as no difference was found for the different antihypertensive drugs used; further, exclusion of subjects treated by beta-blockers did not modify our results. Similarly, a small trial performed in healthy subjects found no effect of beta-blockers on walking speed [37].

This study has several strengths, including its large size, the measure of walking speed using of an automated method, the inclusion of numerous potential confounders in the analyses, and the confirmation of the association in both sexes and in both cross-sectional and longitudinal analyses.

The main limitation of this study is a non-negligible proportion of missing values for walking speed at the fourth follow-up; participants were able to choose if they wanted to be interviewed at home or at the study center and a walking speed could not be measured in those who were interviewed at home or refused to participate. In complete-case analyses (i.e., analyses based on available data), observations with missing information for any of the predictors are deleted from the analyses [38]. This approach reduces the precision of parameter estimates, may introduce bias, and

yields different sample sizes depending on the predictors included in the model. Simple approaches (e.g., missing indicators method) do not in general correct this bias, and require that missingness be independent of the outcome. Multiple imputation is more generally appropriate and allows asymptotically unbiased estimation of exposure effects under the weaker assumption of missing at random conditional on measured variables, including the outcome [38]. This approach is considered to decrease bias without strongly affecting standard errors of regression parameters [39]. In order to assess whether missingness may have biased the association measures, we conducted a sensitivity analysis, by imputing missing values of walking speed based on its main determinants. We found that the associations remained in analyses based on multiple imputation; this finding is reassuring and suggests that missing values were not responsible for an important bias. Another limitation of the study is that, given its observational nature, we were unable to study the consequence of blood pressure control on walking speed decline among treated hypertensive subjects.

In conclusion, hypertension was associated with lower walking speed at baseline and with a higher annual decline in walking speed over follow-up in a large cohort of non-institutionalized elderly individuals. These findings suggest that hypertension plays a role in motor decline in the elderly, partly explained by its consequences on brain vessels. These data are in line with the involvement of hypertension and other vascular risk factors in cognitive decline and dementia. Motor decline in the elderly represents a great challenge for our aging societies, and the optimization of hypertension care may contribute to prevent motor decline and its severe consequences in the elderly.

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Figure legends

Figure 1. Selection of the participants for cross-sectional and longitudinal analyses.

[a] Subjects with a missing value for walking speed at the fourth follow-up, who were included in sensitivity analyses based on multiple imputation.

Table 1 Baseline characteristics of the study population, overall and by tertiles of walking speed and by hypertensive status.

		Tertiles of walking speed				Hypertension[a]		
Characteristics	All	< 1.43 m/s	1.43-1.62 m/s	> 1.62 m/s	p[b]	No	Yes	p[b]
N	3604	1304	1013	1287		1029	2575	
Age, years, mean (SD)	73.4 (4.6)	74.9 (4.6)	73.4 (4.6)	71.9 (4.1)	<0.001	72.2 (4.3)	73.9 (4.7)	<0.001
Women, n (%)	2231 (61.9)	1059 (81.2)	663 (65.5)	509 (39.6)	<0.001	709 (68.9)	1522 (59.1)	<0.001
BMI, $kg.m^{-2}$, mean (SD)	25.7 (4.0)	26.4 (4.5)	25.5 (3.8)	25.1 (3.4)	<0.001	24.3 (3.4)	26.2 (4.1)	<0.001
Low education level, n (%)[c]	1240 (34.3)	618 (47.4)	306 (30.2)	316 (24.6)	<0.001	299 (29.1)	941 (36.5)	0.001
MMSE score, mean (SD)	27.5 (1.9)	27.0 (2.0)	27.6 (1.8)	27.8 (1.7)	<0.001	27.6 (1.9)	27.4 (1.9)	0.001
Depressive symptoms, n (%)[d]	460 (12.9)	225 (17.5)	112 (11.1)	123 (9.6)	<0.001	129 (12.7)	331 (13.0)	0.80
Low physical activity, n (%)[e]	599 (17.3)	291 (23.5)	149 (15.3)	159 (12.6)	<0.001	147 (14.8)	452 (18.3)	0.01
Diabetes mellitus, n (%)	324 (9.2)	123 (9.7)	93 (9.4)	108 (8.7)	0.65	34 (3.4)	290 (11.6)	<0.001
Hypercholesterolemia, n (%)[f]	1422 (40.2)	550 (42.9)	418 (42.0)	454 (36.0)	0.002	343 (33.8)	1079 (42.8)	<0.001
Ex- or current smokers, n (%)	1386 (38.5)	360 (27.6)	376 (37.1)	650 (50.5)	<0.001	352 (34.2)	1034 (40.2)	0.001
Current drinker, n (%)	2844 (79.1)	961 (73.8)	796 (78.8)	1087 (84.7)	<0.001	815 (79.3)	2029 (79.0)	0.92
Psychotropic drugs use, n (%)	911 (25.3)	455 (34.6)	254 (25.1)	206 (16.0)	<0.001	255 (24.8)	656 (25.5)	0.66
NSAIDs for chronic joint pain, n (%)	535 (15.0)	275 (21.4)	123 (12.3)	137 (10.8)	<0.001	138 (13.6)	397 (15.6)	0.12
History of coronary disease, n (%)	369 (10.2)	145 (11.1)	105 (10.4)	119 (9.3)	0.29	34 (3.3)	335 (13.0)	<0.001
Peripheral artery disease, n (%)	112 (3.2)	49 (3.8)	27 (2.7)	36 (2.8)	0.22	20 (2.0)	92 (3.6)	0.01
Exertional dyspnea, n (%)	494 (13.7)	273 (21.0)	119 (11.8)	102 (7.9)	<0.001	106 (10.3)	388 (15.1)	0.01

[a]Antihypertensive treatment or blood pressure ≥ 140/90 mmHg at baseline and first follow-up.

[b]Chi-square statistic for categorical variables or the Student t-test for continuous variables.

[c]Primary without diploma.

[d]Assessed by the Center of Epidemiological Studies–Depression Scale.

[e]Walking less than one hour a day and no sport activity.

[f]Lipid-lowering treatment or cholesterol level ≥ 7.25 mmol/L.

Table 2 Cross sectional association between hypertension and baseline walking speed

Characteristics	N (%)	Walking Speed mean (SD), m/s	Model 1[a] β (SE)	Model 1[a] p	Model 2[b] β (SE)	Model 2[b] p	Model 3[c] β (SE)	Model 3[c] p	Model 4[d] β (SE)	Model 4[d] p
Overall (N=3604)										
No hypertension	1029 (28.6)	1.59 (0.30)	Ref.		Ref.		Ref.		Ref.	
Hypertension[e]	2575 (71.4)	1.51 (0.31)	-0.045 (0.010)	<.001	-0.041 (0.010)	<.001	-0.037 (0.010)	<.001	-0.033 (0.010)	<.001
0 AHD[f]	1780 (49.4)	1.58 (0.30)	Ref.		Ref.		Ref.		Ref.	
1 AHD	1112 (30.9)	1.50 (0.30)	-0.041 (0.010)	<.001	-0.034 (0.010)	.001	-0.028 (0.010)	.005	-0.024 (0.010)	.02
2 AHD	561 (15.5)	1.46 (0.30)	-0.064 (0.013)	<.001	-0.057 (0.013)	<.001	-0.051 (0.013)	<.001	-0.043 (0.013)	.001
≥ 3 AHD	151 (4.2)	1.43 (0.33)	-0.101 (0.022)	<.001	-0.089 (0.022)	<.001	-0.086 (0.023)	<.001	-0.071 (0.023)	.002
P for linear trend				<.001		<.001		<.001		<.001
Men (N=1373)										
No hypertension	320 (23.3)	1.76 (0.29)	Ref.		Ref.		Ref.		Ref.	
Hypertension[e]	1053 (76.7)	1.66 (0.30)	-0.049 (0.018)	.007	-0.051 (0.018)	.006	-0.045 (0.018)	.01	-0.043 (0.018)	.02
Women (N=2231)										
No hypertension	709 (31.8)	1.51 (0.27)	Ref.		Ref.		Ref.		Ref.	
Hypertension[e]	1522 (68.2)	1.40 (0.27)	-0.043 (0.012)	<.001	-0.036 (0.012)	.002	-0.033 (0.012)	.004	-0.030 (0.012)	.01

[a]Adjusted for age, sex, BMI. We present regression coefficients (β) and their standard error (SE).
[b]Additional adjustment for education level, MMSE, physical activity, hypercholesterolemia, smoking, and NSAIDs use for chronic joint pain.
[c]Additional adjustment for depressive symptoms, diabetes mellitus, alcohol and psychotropic drugs use.
[d]Additional adjustment for coronary heart disease, peripheral artery disease, and exertional dyspnea.
[e]Antihypertensive treatment or blood pressure ≥ 140/90 mmHg at baseline and first follow-up.
[f]AHD = antihypertensive drugs.

Table 3 Baseline characteristics of the population included in longitudinal analyses, overall and according to tertiles of walking speed decline

Characteristics	All	Tertiles of annual walking speed decline, cm/s per year			P[a]
		< 0.87	0.87-3.06	>3.06	
N	1774	586	584	604	
Age, years, mean (SD)	71.5 (3.6)	71.2 (3.7)	71.5 (3.6)	71.9 (3.6)	<0.001
Women, n (%)	1092 (61.6)	379 (64.7)	368 (63.0)	345 (57.1)	<0.001
BMI, $kg.m^{-2}$, mean (SD)	25.4 (3.7)	25.0 (3.6)	25.6 (3.6)	25.7 (3.8)	<0.001
Low education level, n (%)[b]	572 (32.2)	197 (33.6)	212 (36.3)	163 (27.0)	<0.001
MMSE score, mean (SD)	27.8 (1.7)	27.8 (1.7)	27.7 (1.8)	27.8 (1.7)	0.48
Depressive symptoms, n (%)[c]	193 (10.9)	68 (11.7)	57 (9.8)	68 (11.3)	0.29
Low physical activity, n (%)d	242 (14.0)	70 (12.2)	83 (14.6)	89 (15.3)	<0.001
Diabetes mellitus, n (%)	138 (7.9)	41 (7.1)	46 (8.0)	51 (8.6)	0.03
Hypercholesterolemia, n (%)[e]	688 (39.3)	239 (41.1)	237 (41.2)	212 (35.7)	0.24
Ex- or current smokers, n (%)	666 (37.5)	196 (33.4)	225 (38.5)	245 (40.6)	0.31
Current drinker, n (%)	1427 (80.7)	475 (81.2)	466 (79.9)	486 (80.9)	0.18
Psychotropic drugs use, n (%)	234 (13.3)	87 (15.0)	80 (13.8)	67 (11.2)	0.004
NSAIDs for chronic joint pain, n (%)	340 (19.2)	116 (19.8)	108 (18.5)	116 (19.2)	0.27
History of coronary disease, n (%)	137 (7.7)	37 (6.3)	50 (8.6)	50 (8.3)	0.08
Peripheral artery disease, n (%)	31 (1.8)	8 (1.4)	11 (1.9)	12 (2.0)	0.43
Exertional dyspnea, n (%)	173 (9.8)	55 (9.4)	58 (9.9)	60 (9.9)	0.006
Baseline walking speed, m/s, mean (SD)	1.61 (0.29)	1.50 (0.25)	1.58 (0.26)	1.74 (0.30)	<0.001

[a]Adjusted for baseline walking speed.
[b]Primary without diploma.
[c]Assessed by the Center of Epidemiological Studies–Depression Scale.
[d]Walking less than one hour a day and no sport activity.
[e]Lipid-lowering treatment or cholesterol level ≥ 7.25 mmol/L.

Table 4 Longitudinal association between hypertension and annual decline in walking speed

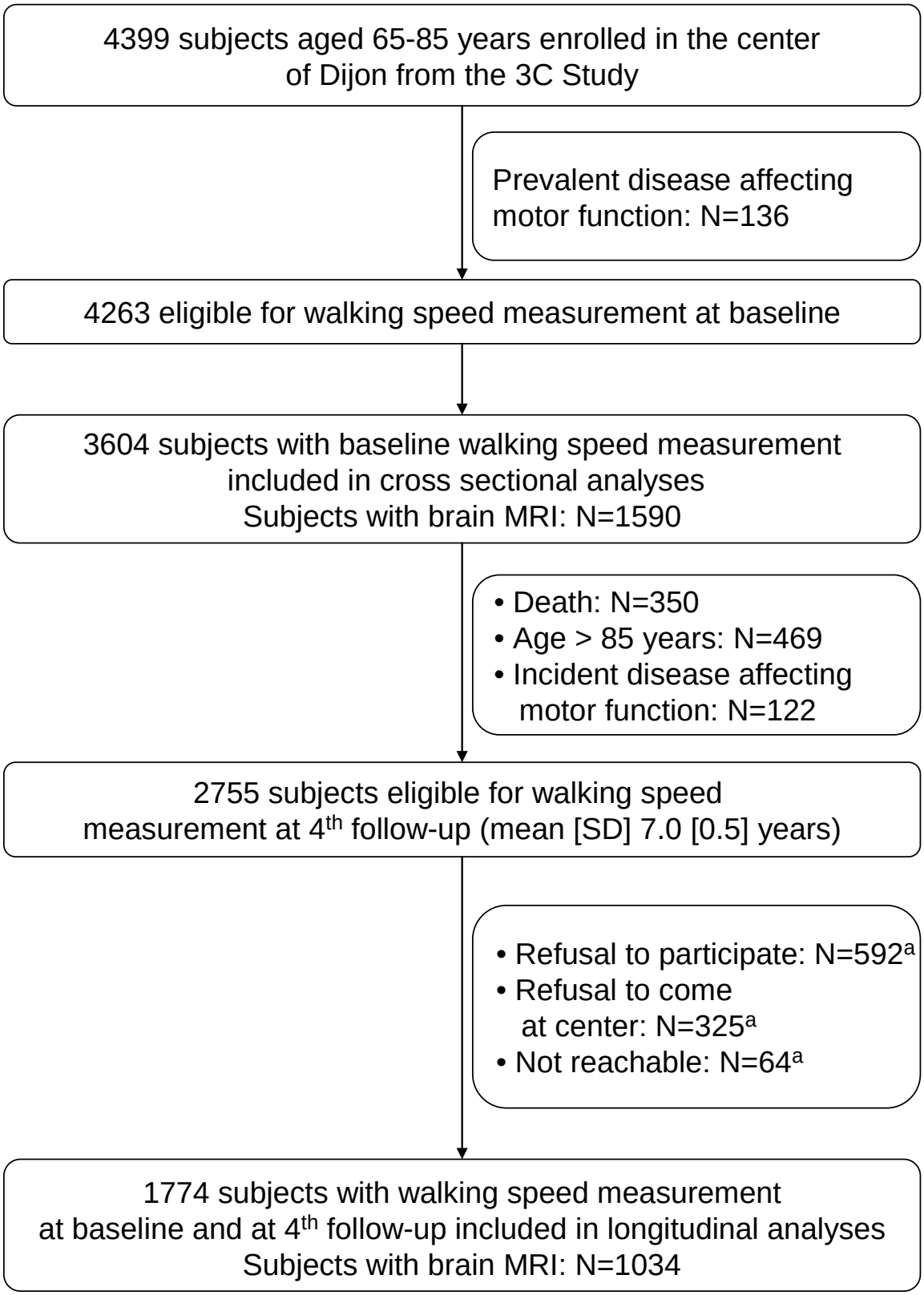
Characteristics	N, %	Mean (SD) annual walking speed decline, cm/s/yr	Model 1[a]		Model 2[b]		Model 3[c]	
			β (SE)	p	β (SE)	p	β (SE)	p
Overall (N=1774)								
No hypertension	603 (34.0)	1.87 (3.3)	Ref.		Ref.		Ref.	
Hypertension[d]	1171 (66.0)	2.30 (3.4)	0.44 (0.15)	0.004	0.43 (0.16)	0.006	0.37 (0.16)	0.02
0 AHD[e]	1026 (57.8)	1.99 (3.31)	Ref.		Ref.		Ref.	
1 AHD	497 (28.0)	2.38 (3.34)	0.47 (0.16)	0.004	0.40 (0.17)	0.02	0.33 (0.17)	0.06
≥ 2 AHD	251 (14.2)	2.38 (3.58)	0.60 (0.21)	0.004	0.59 (0.22)	0.006	0.52 (0.22)	0.02
P for linear trend				<0.001		0.002		0.01
Men (N=682)								
No hypertension	183 (26.8)	1.95 (3.7)	Ref.		Ref.		Ref.	
Hypertension[d]	499 (73.2)	2.51 (3.6)	0.49 (0.27)	0.07	0.55 (0.28)	0.05	0.44 (0.28)	0.12
Women (N=1092)								
No hypertension	420 (38.5)	1.83 (3.18)	Ref.		Ref.		Ref.	
Hypertension[d]	672 (61.5)	2.15 (3.18)	0.39 (0.18)	0.03	0.38 (0.19)	0.05	0.34 (0.19)	0.08

[a]Adjusted for baseline walking speed, age, sex, BMI. We present regression coefficients (β) and their standard error (SE).
[b]Additional adjustment for education level, MMSE, hypercholesterolemia, smoking, baseline physical activity level, diabetes mellitus, and psychotropic drug use.
[c]Additional adjustment for coronary heart disease, peripheral artery disease, and exertional dyspnea.
[d]Antihypertensive treatment or blood pressure ≥ 140/90 mmHg at baseline and first follow-up.
[e]AHD = antihypertensive drugs.

Table 5 Relationship between hypertension and baseline walking speed or walking speed decline among subjects who performed a brain MRI at baseline

		Model 1[a]		Model 2[b]	
	N (%)	β (SE)	p	β (SE)	p
Cross-sectional analyses[c]					
No hypertension	505 (31.8)	Ref.		Ref.	
Hypertension[d]	1085 (68.2)	-0.043 (0.017)	0.01	-0.036 (0.017)	0.03
Longitudinal analyses[e]					
No hypertension	375 (36.3)	Ref.		Ref.	
Hypertension[d]	659 (63.7)	0.38 (0.19)	0.04	0.31 (0.19)	0.10

[a]Adjusted for age, sex, and BMI.
[b]Additional adjustment for volume of white matter lesions (WML) (log transformed) and presence of lacunar infarcts
[c]Relation between hypertensive status and baseline walking speed.
[d]Antihypertensive treatment or blood pressure ≥ 140/90 mmHg at baseline and first follow-up.
[e]Relation between hypertensive status and walking speed change over follow-up. Models are also adjusted for baseline walking speed.


4399 subjects aged 65-85 years enrolled in the center of Dijon from the 3C Study
Prevalent disease affecting motor function: N=136
4263 eligible for walking speed measurement at baseline
3604 subjects with baseline walking speed measurement included in cross sectional analyses
Subjects with brain MRI: N=1590
• Death: N=350
• Age > 85 years: N=469
• Incident disease affecting motor function: N=122
2755 subjects eligible for walking speed measurement at 4th follow-up (mean [SD] 7.0 [0.5] years)
• Refusal to participate: N=592a
• Refusal to come at center: N=325a
• Not reachable: N=64a
1774 subjects with walking speed measurement at baseline and at 4th follow-up included in longitudinal analyses
Subjects with brain MRI: N=1034