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ORIGINAL RESEARCH

GERIATRIC CARDIOLOGY

Association Between Pulse Wave Velocity and Frailty, Disability, and Mortality in Community-Dwelling Older Adults

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ABSTRACT

BACKGROUND Arterial stiffness leads to several adverse events in the older population, but there is a lack of data on its association with frailty, disability, and mortality in the same population.

OBJECTIVES The purpose of this study was to evaluate the role of arterial stiffness in the loss of functional ability (frailty and disability) and mortality.

METHODS Data were taken from community-dwelling aged 65 years participants without diabetes in the Toledo Study of Healthy Ageing cohort. Pulse wave velocity (PWV), assessed through SphygmoCor, was recorded at baseline. Median follow-up time were 2.99 years for frailty (frailty phenotype [FP] and Frailty Trait Scale-5 [FTS5]) and disability (Katz Index) and 6.2 for mortality. Logistic regressions models were built for disability and frailty and Cox proportional hazards model for death, adjusted by age and sex, comorbidity, cardiovascular risk factors, asymmetric dimethylarginine levels, and polypharmacy.

RESULTS Overall, 978 (mean age 74.5 ± 5.6 years, 56.7% female) participants were included. Different cut-off points were shown for each outcome. PWV >11.5 m/s was cross-sectionally associated with frailty (FP: OR fully-adjusted model: 1.69, 95% CI: 1.45-1.97; FTS5: OR: 1.51, 95% CI: 1.22-1.87) and disability (OR: 1.51, 95% CI: 1.26-1.79); PWV >10 m/s with incident frailty by FP (OR: 1.36, 95% CI: 1.10-1.68) and FTS5 (OR: 1.40, 95% CI: 1.12-1.75), and PWV >11 m/s with death (HR: 1.28, 95% CI: 1.09-1.50). For incident (OR: 1.28, 95% CI: 1.06-1.55) and worsening disability (OR: 1.21, 95% CI: 1.02-1.45) the threshold was 12.5 m/s. Below these cut-off points, age was the best predictor of adverse outcomes.

CONCLUSIONS Arterial stiffness predicts frailty, disability, and mortality in older people, with different cut-off points, ie,severity degrees, for each of the assessed outcomes. (JACC Adv 2023;2:100423) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ADMA = asymmetric dimethylarginine

BADL = basic activities of daily living

DEXA = dual-energy x-ray absorptiometry

FP = frailty phenotype

FTS5 = Frailty Trait Scale-5

HOMA-IR = Homeostasis Model Assessment of Estimated Insulin Resistance

OR = odds ratio

PWV = pulse wave velocity

Aging is usually accompanied by an increase in arterial stiffness,[1,2] that jointly to other risk factors (diabetes, hypertension, dyslipidemia) is a main contributor to the development of cardiovascular diseases, the leading cause of morbimortality in the world.[3] This loss of elastic capacity of the large arteries seems to be an early biomarker of changes in the arterial walls closely related to the individual's biological age.[4]

However, its role in the etiology of the reduction of physical function associated with aging process is controversial, while multifactorial and individually specific.[5] Frailty is an age-associated biological syndrome that decrease the individual physiological reserves when facing minor stressors.[6] The assessment and identification of underlying risk factors for frailty syndrome and its development could not only prevent frailty, but also some of its adverse consequences, such cardiovascular diseases outcomes,[5] disability, or mortality.[7-9] Vascular system dysfunction has been one of the postulated pathogenic pathways leading to frailty,[8,10] since its early stages.[10] However, available results are inconsistent,[11] coming from separate cohorts, and no study has explored the longitudinal association between arterial stiffness and both frailty and disability in the same cohort.[12] A noninvasive index acknowledged as the "gold-standard" for assessing central arterial stiffness is pulse wave velocity (PWV).[13,14] Our study aims to assess the role of PWV, as a biomarker of arterial stiffness, on adverse events linked to functioning in older adults, both cross-sectionally and longitudinally, plus death, in a single cohort of older people living in the community.

Furthermore, the identification of cut-off points for establishing levels of risk is of the utmost relevance. Entities like the European Society of Hypertension proposed a fixed threshold of 10 m/s to identify individuals with high risk of cardiovascular risk factors.[14] However, some studies have suggested that this value could depend on the outcome event or the population studied.[15-17] Moreover, the relationship between PWV and the risk of some outcomes may not be linear.[18] Therefore, we also address this controversy by assessing the cut-off points for the association (if any) between arterial stiffness and the 3 outcomes assessed (frailty, disability, and death).

MATERIALS AND METHODS

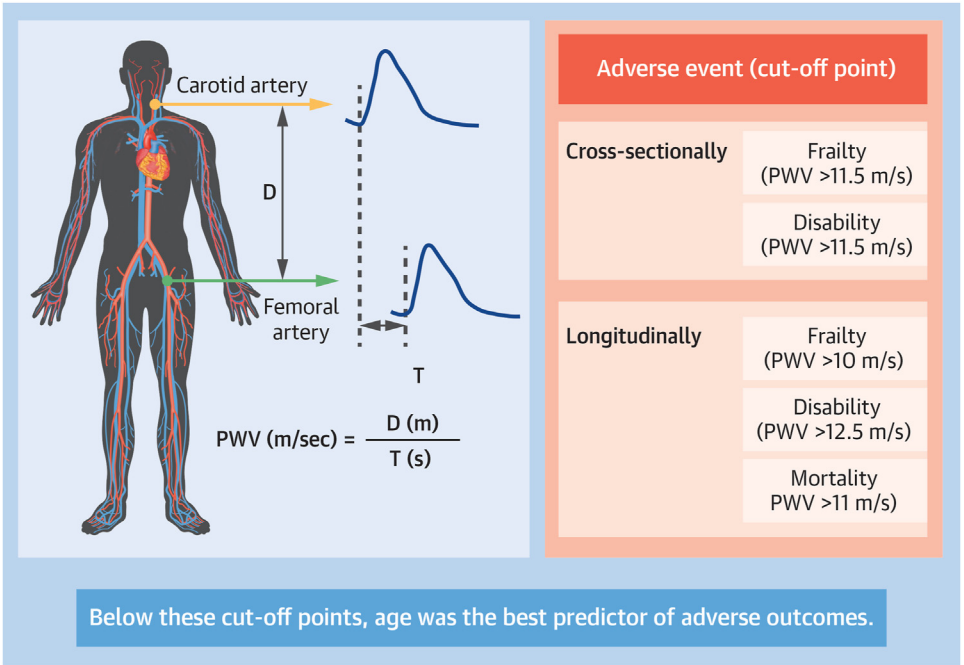
Participant's data were taken from the Toledo Study of Healthy Aging (TSHA).[19] TSHA is a prospective cohort study, designed to analyze determinants of frailty in community-dwelling individuals older than 65 years living in the province of Toledo, Spain. The study protocol was approved by the Clinical Research Ethics Committee of the Toledo Hospital Complex, Spain. All participants signed informed consent prior to data acquisition. For the current analysis we used the baseline data from the second wave (2011-2013). The outcomes frailty and disability were assessed during the third wave (2015-2017) after a median follow-up of 2.99 years (range 2.0-5.4 years). Mortality was assessed after a median follow-up of 6.2 years (range 1-7.5) through the Spanish National Death Index. All subjects without diabetes and with the functional variables appropriately evaluated at baseline were included.

For the statistical analysis, only the participants without missing data of all the covariates were included, yielding a total number of 978 subjects. There were no differences between those excluded for the analysis (118) and the final sample regarding age (74.5 ± 5.63 years in the final sample vs 74.95 ± 6.09 in those excluded; $P = 0.517$), sex (56.65% females vs 54.24%; $P = 0.618$), frailty phenotype (FP) (71.57% robust vs 69.49%; $P = 0.881$), Frailty Trait Scale-5 (FTS5) mean score (14.89 ± 7.04 vs 15.67 ± 6.73; $P = 0.140$), percentage of dependence for basic activities of daily living (BADL) (14.60% vs 16.38%; $P = 0.609$), and comorbidity by the Charlson Index (0.93 ± 1.47 vs 0.79 ± 1.36; $P = 251$).

STUDY VARIABLES. Pulse wave velocity. Arterial stiffness was evaluated by assessing central PWV with a SphygmoCor (Actor Medical), following the protocol proposed by Laurent et al.[20] Briefly, PWV was measured after 5-minute rest in the supine position at 21 to 25 °C of room temperature. The measurements were recorded between 9:00 AM and 12:00 AM to minimize diurnal variation effects. Subject weight and height were also recorded.

PWV was automatically calculated as the distance travelled by the pulse wave from the carotid to the femoral artery (in meters) divided by the time interval (in seconds). With this purpose, the proximal distance between the carotid pulse and sternal manubrium is measured. The distal distance is estimated between the femoral pulse located in the inner third of the inguinal crease and the sternal manubrium (**Central Illustration**). The PWV was measured twice, and the average of both measurements was analyzed. Performance of at least 2 measurements was required for inclusion in the analysis. If the difference between the 2 measurements was higher than 0.5 m/s, a third

CENTRAL ILLUSTRATION **Association Between PWV and Frailty, Disability, and Mortality in Community-Dwelling Adults Older Than 65 Years of Age**



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Arterial stiffness was evaluated by assessing central pulse wave velocity (PWV) and was strongly associated with age. Segmented regression was used to identify PWV cut-off points associated with adverse outcomes (frailty, disability, and mortality). Different PWV cut-off points were identified for each of the outcomes. In those subjects with a PWV values over the cut-off point, PWV independently predicted the outcome. Conversely, in those subjects with PWV less than the cut-off point, age was the main determinant of outcome. D = distance; T = time.

measurement was taken. The median value of PWV was finally recorded.[21]

FRAILTY AND DISABILITY

Frailty status was assessed according to the FP[7] fitted to the Spanish population[22] (Supplemental Table 1) and the FTS5[9] (Supplementary Table 2). Frailty was assessed at baseline (wave 2) and at the follow-up period (wave 3). BADL were evaluated by the Katz Index.[23] Transitions of a score of 6 to 5 or less in the Katz Index at follow-up were considered as incident disability.

MORTALITY

Vital status and death dates were ascertained through the Spanish National Death Index (Ministry of Health, Consumer Affairs and Social Welfare). Participants were followed up to March 2019 or until death.

CONFOUNDING VARIABLES. Self-reported smoking data were used to inform 2 categories of participants: yes (if smoked for at least 1 year) or no (never smoked). Charlson Index[24] was used to assess co-morbidity. Body composition was assessed at wave 2. Muscle and fat mass were determined using dual-energy x-ray absorptiometry (DEXA) (Hologic, Serie Discovery QDR). DEXA scans were analyzed using the software Physician's Viewer (apex System Software, version 3.1.2). DEXA findings were used to estimate the total muscle and fat mass, appendicular muscle and fat mass, fat percentage, and to obtain the ratio between muscle/fat mass. Polypharmacy was defined as the regular intake of ≥5 drugs per day. Plasma insulin was measured by electrochemiluminescence immunoassay using a module Cobas e801 (Roche diagnostics GmbH). Insulin resistance was calculated according to the homeostasis model assessment of insulin resistance (HOMA-IR) as follows: fasting insulin (U/L) ×

TABLE 1 Demographic Characteristics According to the Different PWV Cut-Off Points

	All (N = 978)	PWV ≤10 (n = 688)	PVW >10 (n = 290)	*P* Value	PWV ≤11 (n = 796)	PWV >11 (n = 182)	*P* Value
Age, y	74.50 ± 5.63	73.35 ± 5.08	77.22 ± 5.95	**<0.001**	73.81 ± 5.31	77.52 ± 6.02	**<0.001**
Female	554 (56.65)	406 (59.01)	148 (51.03)	**0.022**	467 (58.67)	87 (47.80)	**0.008**
Frailty phenotype							
Robust	700 (71.57)	509 (73.98)	191 (65.86)	**0.017**	587 (73.74)	113 (62.09)	**0.003**
Prefrail	257 (26.28)	163 (23.69)	94 (32.41)		191 (23.99)	66 (36.26)	
Frail	21 (2.15)	16 (2.33)	5 (1.72)		18 (2.26)	3 (1.65)	
Frail Trait Scale-5							
Frail	84 (8.59)	48 (6.98)	36 (12.41)	**0.006**	58 (7.29)	26 (14.29)	**0.002**
Disability							
Dependence in BADL	141 (14.60)	87 (12.78)	54 (18.95)	**0.013**	105 (13.36)	36 (20.00)	**0.023**
Katz Index	5.83 ± 0.46	5.86 ± 0.41	5.77 ± 0.55	**0.007**	5.85 ± 0.41	5.74 ± 0.62	**0.003**
DEXA parameters							
Lean/fat ratio	1.83 ± 0.75	1.82 ± 0.76	1.85 ± 0.73	0.540	1.82 ± 0.76	1.86 ± 0.70	0.506
Comorbidities and drugs							
Charlson Index	0.93 ± 1.47	0.97 ± 1.49	0.85 ± 1.44	0.272	0.97 ± 1.53	0.77 ± 1.19	0.100
Number of drugs	4.37 ± 2.72	4.34 ± 2.71	4.45 ± 2.74	0.553	4.33 ± 2.70	4.58 ± 2.80	0.260
Polypharmacy	439 (44.89)	302 (43.90)	137 (47.24)	0.337	348 (43.72)	91 (50.00)	0.124
Death							
Death	119 (12.17)	73 (10.61)	46 (15.86)	**0.022**	91 (11.43)	28 (15.38)	0.141
IR-HOMA	3.21 ± 2.20	3.12 ± 2.22	3.42 ± 2.13	0.052	3.13 ± 2.19	3.54 ± 2.20	**0.023**
Creatinine	0.88 ± 0.26	0.86 ± 0.23	0.93 ± 0.31	**<0.001**	0.86 ± 0.24	0.95 ± 0.32	**<0.001**
Systolic blood pressure	151.21 ± 20.31	148.04 ± 18.53	158.74 ± 22.30	**<0.001**	148.94 ± 19.15	161.17 ± 22.19	**<0.001**
Diastolic blood pressure	85.55 ± 10.50	84.53 ± 10.18	87.96 ± 10.86	**<0.001**	84.85 ± 10.28	88.62 ± 10.93	**<0.001**
PWV, m/s	9.17 ± 2.31	7.97 ± 1.24	12.00 ± 1.70	**<0.001**	8.32 ± 1.44	12.89 ± 1.56	**<0.001**
Smoking status	309 ± 31.60	216 ± 31.40	93 ± 32.07	0.836	246 ± 30.90	63 ± 34.62	0.331

TABLE 1 Continued

	PWV ≤11.5 (n = 831)	PWV >11.5 (n = 147)	*P* Value	PWV ≤12.5	PWV >12.5 (n = 86)	*P* Value
Age, y	73.91 ± 5.36	77.84 ± 6.00	**<0.001**	74.20 ± 5.47	77.56 ± 6.44	**<0.001**
Female	481 (57.88)	73 (49.66)	0.064	513 (57.51)	41 (47.67)	0.079
Frailty phenotype						
Robust	609 (73.29)	91 (61.90)	**0.014**	652 (73.09)	48 (55.81)	**0.003**
Prefrail	204 (24.55)	53 (36.05)		221 (24.78)	36 (41.86)	
Frail	18 (2.17)	3 (2.04)		19 (2.13)	2 (2.33)	
Frail Trait Scale-5						
Frail	62 (7.46)	22 (14.97)	**0.003**	70 (7.85)	14 (16.28)	**0.008**
Disability						
Dependence in BADL	113 (13.78)	28 (19.18)	0.089	124 (14.07)	17 (20.00)	0.140
Katz Index	5.85 ± 0.41	5.73 ± 0.66	**0.006**	5.84 ± 0.43	5.71 ± 0.69	**0.009**
DEXA parameters						
Lean/fat ratio	1.83 ± 0.76	1.85 ± 0.69	0.678	1.82 ± 0.75	1.91 ± 0.71	0.310
Comorbidities and drugs						
Charlson Index	0.95 ± 1.51	0.82 ± 1.24	0.334	0.95 ± 1.50	0.77 ± 1.11	0.280
Number of drugs	4.35 ± 2.72	4.50 ± 2.71	0.526	4.37 ± 2.73	4.44 ± 2.57	0.804
Polypharmacy	370 (44.52)	69 (46.94)	0.588	402 (45.07)	37 (43.02)	0.716
Death						
Death	97 (11.67)	22 (14.97)	0.260	105 (11.77)	14 (16.28)	0.222
IR-HOMA	3.14 ± 2.17	3.58 ± 2.31	**0.027**	3.20 ± 2.23	3.28 ± 1.86	0.743
Creatinine	0.87 ± 0.24	0.95 ± 0.34	**<0.001**	0.87 ± 0.25	0.98 ± 0.35	**<0.001**
Systolic blood pressure	149.30 ± 19.30	162.03 ± 22.42	**<0.001**	150.01 ± 19.62	163.65 ± 23.09	**<0.001**
Diastolic blood pressure	84.92 ± 10.23	89.10 ± 11.27	**<0.001**	85.20 ± 10.23	89.20 ± 12.46	**0.001**
PWV, m/s	8.44 ± 1.53	13.28 ± 1.49	**<0.001**	8.69 ± 1.74	14.18 ± 1.34	**<0.001**
Smoking status	260 (31.29)	49 (33.33)	0.623	275 (30.83)	34 (39.53)	0.097

Values are mean ± SD or n (%). $P < 0.05$.

BADL = Basic Activities of Daily Living; DEXA = dual-energy x-ray absorptiometry; HOMA-IR = Homeostasis Model Assessment of Estimated Insulin Resistance; PWV = pulse wave velocity.

fasting glucose (mmol/L)/22.5.[25] HOMA-IR was natural log transformed given its skewed distribution. One unit increment in log HOMA-IR was considered to compute HRs and odds ratios (ORs). This value was obtained in the second wave of the study. Circulating asymmetric dimethylarginine (ADMA) was determined in plasma from participants of the second wave of TSHA. Samples were assessed in duplicate by using specific enzyme-linked immunosorbent assay commercial kits (ADMA: cat# E-EL-0042, assay range: 0.077-4.944 μM and assay sensitivity: 0.046 μM), Elabscience; following manufacturers' instructions.

STATISTICAL ANALYSIS. Descriptive statistics are presented as mean (SD) for continuous variables and number (N, %) for discrete and categorical variables. Differences between groups were tested using Mann-Whitney and Chi-square test.

Logistic regressions were used for frailty (FTS5: no frail vs frail; FP: robust vs prefrail-or-frail) and disability (Katz Scale 6 vs <6). Incident frailty was defined as the transition from non-frail to frail (FTS-5) or from robust to prefrail-or-frail (FP) when frailty was reassessed at the end of the follow-up period. Transitions of a score of 6 to 5 or less in the Katz Index at follow-up were considered as incident disability. Worsening disability was defined as a loss of ≥1 point during the same time-period. Cox proportional hazards model were built for death. Models were adjusted by age and sex, comorbidity, cardiovascular risk factors, ADMA levels, and polypharmacy.

In the study population, PWV was strongly associated with age,[26,27] except at the upper extreme. Therefore, a model that included both variables (PWV and age) jointly was used. To assess their relationship with the outcomes (events), segmented regression was used and the PWV cut-off points were determined considering the Youden's Index.[28,29] Precision metrics of PWV cut-off points for the different adverse outcomes is shown in Supplemental Table 3.

To assess the effect of the main variables on the adverse events, different types of multivariate regression models were used depending on the available data. Model 1 was the unadjusted model. Model 2 was adjusted for sex and Charlson Index. Model 3 included Model 2 variables plus smoking status, systolic blood pressure, muscle/fat ratio, and ADMA levels. Model 4 included Model 3 variables plus creatinine levels, polypharmacy, and log (HOMA-IR). Models 5 added frailty status at baseline according to the FP (Model 5a) or the FTS5 (Model 5b). Models 6 added disability in BADL to Model 4, depending on whether (Model 6a) or not (Model 6b) the incontinence item was included.

Analyses were performed using the statistical package R for Windows version 3.6.1, and a P value of < 0.05 was considered statistically significant in all analyses.

RESULTS

Overall, 978 subjects (mean age 74.50 ± 5.63 years; 56.65% female) were included. Participant characteristics of the whole sample and for the different cut-off points of the PWV are also shown in **Table 1**.

CROSS-SECTIONAL ASSOCIATION OF PWV AND AGE WITH FUNCTIONAL STATUS IN OLDER SUBJECTS. To evaluate the association between PWV and the prevalence of frailty and disability for BADL, the estimated PWV cut-off point was 11.5 m/s (**Table 2**). PWV was associated with prevalent frailty assessed by the FP [OR range from 1.69 (95% CI: 1.45-1.97) in the fully adjustment model (M4) to 1.77 (95% CI: 1.53-2.04) in the nonadjusted model (M1); $P < 0.001$]. These findings were also observed when FTS5 was used to assess frailty [OR from 1.51 (95% CI: 1.22-1.87) in M4 to 1.61 (95% CI: 1.33-1.94) in M1; $P < 0.001$]. Similar results were obtained when disability was explored. PWV higher than 11.5 m/s was cross-sectionally associated with a higher risk of being dependent for BADL in all models of adjustments [OR range from 1.51 (95% CI: 1.26-1.79) to 1.54 (95% CI: 1.32-1.81); $P < 0.001$]. Age was not significantly associated with frailty or disability in any model explored over the cut-off point.

In contrast, in older adults with a PWV ≤11.5 m/s, age but not PWV was the variable associated with the adverse events. Age increased the risk of being frail, assessed through the FP [OR: 1.09 (95% CI: 1.06-1.14) in M4; OR: 1.10 (95% CI: 1.06-1.14) in M1]. This finding was also present with FTS5, although in this case only the unadjusted model was significant. Association was also shown when disability was explored [OR ranges from 1.09 (95% CI: 1.04-1.14) in M4 to 1.10 (95% CI: 1.05-1.14) in M1].

LONGITUDINAL ASSOCIATION OF PWV AND AGE WITH ADVERSE EVENTS IN OLDER SUBJECTS. The association between PWV and age and adverse outcomes was assessed and demonstrated different PWV cut-off points linked to the different outcomes. Again, in those subjects with a PWV over the cut-off point, PWV independently predicted the adverse event, while in those with a PWV lower than the cut-off point, age, but not PWV, was the main risk factor associated to majority of the outcomes.

TABLE 2 Cross-Sectional Association of PWV and Age With Functional Status (Frailty and Disability) in Nondiabetic Community-Dwelling Older Subjects

		PWV >11.5 m/s				PWV ≤11.5 m/s			
		PWV		Age		PWV		Age	
	Model	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Frail (frailty phenotype)									
	Model 1	1.77 (1.53-2.04)	**<0.001**	1.00 (0.98-1.02)	0.597	0.97 (0.87-1.08)	0.931	1.10 (1.06-1.14)	**<0.001**
	Model 2	1.79 (1.55-2.06)	**<0.001**	1.00 (0.98-1.02)	0.620	0.97 (0.87-1.08)	0.986	1.11 (1.07-1.15)	**<0.001**
	Model 3	1.75 (1.50-2.03)	**<0.001**	1.00 (0.98-1.02)	0.626	0.97 (0.87-1.09)	0.984	1.10 (1.06-1.14)	**<0.001**
	Model 4	1.69 (1.45-1.97)	**<0.001**	1.00 (0.98-1.02)	0.547	0.97 (0.86-1.08)	0.944	1.09 (1.06-1.14)	**<0.001**
Frail (FTS5)									
	Model 1	1.61 (1.33-1.94)	**<0.001**	0.97 (0.94-1.01)	0.360	0.92 (0.77-1.10)	0.134	1.06 (1.01-1.12)	**0.029**
	Model 2	1.61 (1.33-1.95)	**<0.001**	0.97 (0.94-1.01)	0.602	0.95 (0.80-1.14)	0.127	1.05 (1.00-1.11)	0.055
	Model 3	1.60 (1.31-1.97)	**<0.001**	0.97 (0.93-1.01)	0.527	0.94 (0.78-1.13)	0.097	1.05 (1.00-1.11)	0.065
	Model 4	1.51 (1.22-1.87)	**<0.001**	0.97 (0.93-1.01)	0.600	0.95 (0.79-1.15)	0.101	1.04 (0.98-1.10)	0.160
Disability (BADL)									
	Model 1	1.54 (1.32-1.81)	**<0.001**	1.00 (0.98-1.03)	0.073	0.88 (0.77-1.01)	0.802	1.10 (1.05-1.14)	**<0.001**
	Model 2	1.55 (1.32-1.83)	**<0.001**	1.00 (0.98-1.03)	0.116	0.90 (0.78-1.03)	0.732	1.10 (1.05-1.15)	**<0.001**
	Model 3	1.58 (1.33-1.87)	**<0.001**	1.00 (0.97-1.03)	0.149	0.90 (0.78-1.04)	0.836	1.10 (1.05-1.15)	**<0.001**
	Model 4	1.51 (1.26-1.79)	**<0.001**	1.00 (0.97-1.03)	0.152	0.90 (0.78-1.04)	0.924	1.09 (1.04-1.14)	**<0.001**

Model 1: Unadjusted model. Model 2: adjusted by sex and Charlson Index. Model 3: Model 2 plus smoking status, systolic blood pressure, muscle/fat ratio, and asymmetric dimethylarginine levels. Model 4: Model 3+ creatinine levels, polypharmacy, and log (Homeostasis Model Assessment of Insulin Resistance). **Bold** values indicate the statistical significance of the associations.

BADL = basic activities of daily living; FTS5 = Frailty Trait Scale-5; PWV = pulse wave velocity.

Among nonfrail participants (n = 957 FP, 894 FTS5) at baseline, 106 (FP) and 51 (FTS5) became frail at follow-up. The PWV cut-off point for incident frailty was 10 m/s (Table 3). PWV >10 was associated with incident frailty in those who were identified as robust according to the FP [OR range from 1.36 (95% CI: 1.10-1.68) in M4 to 1.36 (95% CI: 1.12-1.65) in M1; $P < 0.01$ for all) (Figure 1B), or nonfrail according to the FTS5 (OR from 1.40 (95% CI: 1.12-1.75) in M4 to 1.44 (95% CI: 1.18-1.76) in M1; $P < 0.01$ for all] (Figure 1D). On the other hand, in subjects whose PWV ≤10 m/s, age but not PWV was significantly associated with the development of frailty (Figures 1A and 1C).

Among nondisabled participants (n = 837) at the time of the first evaluation, 181 became disabled at follow up. In the entire sample, 193 disability score became worse, according to the Katz Index. For both incident and worsening disability, the PVW threshold was 12.5 m/s. PWV >12.5 m/s increased the risk of incident disability [OR range from 1.28 (95% CI: 1.06-1.55) in M5a to 1.35 (95% CI: 1.14-1.59) in M1; $P < 0.05$ for all] and worsening disability [OR ranges from 1.21 (95% CI: 1.02-1.45) in M5b to 1.28 (95% CI: 1.10-1.50); $P < 0.05$ for all] (Figure 1F). In this particular case, age was not able to predict neither worsening disability nor incident disability in the fully adjusted models in those subjects with PWVs below the cut-off point.

The cut-off point for mortality was a PWV of 11.0 m/s (Table 4). Having a PWV >11 m/s was an independent significant predictor of death [HR ranges from 1.28 (95% CI: 1.09-1.50) in M5a to 1.37 (95% CI: 1.19-1.58) in M1; $P < 0.005$] for all the models explored (Figure 2B). For these models, in older adults whose PWV was ≤11 m/s, age was significantly associated with mortality [HR ranges from 1.05 (95% CI: 1.01-1.10) in M5a to 1.06 (95% CI: 1.02-1.11) in M1; $P < 0.05$] (Figure 2A).

DISCUSSION

This is one of the few studies showing the value of PWV (considered the gold standard for assessing arterial stiffness)[13,14] as a predictor of adverse functional outcomes (frailty and disability), both cross-sectionally and longitudinally in community-dwelling older adults. We demonstrated that the cut-off points of PWV differ depending on the outcome (eg, lowest cut-off for frailty (10 m/s), highest for disability (12.5 m/s), thus suggesting a dose-response relationship along the pathway of functional decline. For the outcomes explored, below these thresholds, age was a more powerful factor than PWV. In this regard it is noteworthy that thresholds are different for each considered outcome in our study, similar to that observed in studies on more

TABLE 3 Longitudinal Association of PWV and Age With Functional Status (Frailty and Disability) in Nondiabetic Community-Dwelling Older Subjects

		PWV		Age		PWV		Age	
	Model	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Frailty		PWV >10 m/s				PWV ≤10 m/s			
Incident frailty (fried)									
	Model 1	1.36 (1.12-1.65)	**0.002**	1.03 (1.00-1.06)	0.065	0.95 (0.78-1.16)	0.612	1.09 (1.03-1.14)	**0.001**
	Model 2	1.38 (1.13-1.68)	**0.001**	1.03 (1.00-1.06)	0.055	0.94 (0.77-1.15)	0.544	1.09 (1.04-1.15)	**0.001**
	Model 3	1.38 (1.13-1.70)	**0.002**	1.03 (1.00-1.07)	**0.033**	0.95 (0.77-1.18)	0.660	1.09 (1.04-1.15)	**0.001**
	Model 4	1.36 (1.10-1.68)	**0.005**	1.03 (1.00-1.07)	0.051	0.95 (0.77-1.18)	0.654	1.09 (1.03-1.15)	**0.002**
Incident frailty (FTS5)									
	Model 1	1.44 (1.18-1.76)	**<0.001**	1.03 (0.99-1.07)	0.189	1.15 (0.85-1.56)	0.370	1.07 (1.00-1.14)	**0.041**
	Model 2	1.45 (1.19-1.78)	**<0.001**	1.03 (0.99-1.08)	0.135	1.16 (0.86-1.58)	0.331	1.07 (1.00-1.15)	**0.039**
	Model 3	1.42 (1.15-1.77)	**0.001**	1.03 (0.99-1.08)	0.171	1.19 (0.87-1.65)	0.280	1.06 (0.99-1.14)	0.079
	Model 4	1.40 (1.12-1.75)	**0.003**	1.03 (0.99-1.08)	0.153	1.21 (0.87-1.68)	0.257	1.06 (0.99-1.14)	0.092
Disability		PWV >12.5 m/s				PWV ≤12.5 m/s			
Incident disability									
	Model 1	1.35 (1.14-1.59)	**<0.001**	0.99 (0.97-1.02)	0.490	0.96 (0.86-1.07)	0.563	1.06 (1.02-1.11)	**0.007**
	Model 2	1.34 (1.14-1.58)	**0.001**	0.99 (0.97-1.02)	0.668	0.98 (0.87-1.09)	0.546	1.06 (1.01-1.11)	**0.012**
	Model 3	1.34 (1.12-1.61)	**0.002**	0.99 (0.96-1.02)	0.690	0.98 (0.87-1.10)	0.501	1.06 (1.01-1.11)	**0.016**
	Model 4	1.31 (1.09-1.58)	**0.004**	0.99 (0.96-1.02)	0.859	0.99 (0.88-1.11)	0.516	1.05 (1.00-1.10)	**0.034**
	Model 5a	1.28 (1.06-1.55)	**0.010**	0.99 (0.96-1.02)	0.899	0.99 (0.88-1.12)	0.491	1.05 (1.00-1.10)	0.059
	Model 5b	1.28 (1.06-1.55)	**0.011**	0.99 (0.96-1.02)	0.897	0.99 (0.88-1.12)	0.511	1.05 (1.00-1.10)	0.058
Worsening disability									
	Model 1	1.28 (1.10-1.50)	**0.001**	0.99 (0.96-1.01)	0.525	0.97 (0.87-1.07)	0.32	1.05 (1.00-1.09)	**0.032**
	Model 2	1.27 (1.09-1.49)	**0.002**	0.99 (0.96-1.01)	0.670	0.98 (0.88-1.09)	0.316	1.04 (1.00-1.08)	**0.049**
	Model 3	1.28 (1.08-1.51)	**0.005**	0.99 (0.96-1.01)	0.786	0.99 (0.88-1.10)	0.285	1.04 (1.00-1.08)	0.068
	Model 4	1.24 (1.04-1.48)	**0.015**	0.99 (0.96-1.01)	0.959	1.00 (0.89-1.11)	0.285	1.03 (0.99-1.08)	0.135
	Model 5a	1.23 (1.03-1.47)	**0.026**	0.99 (0.96-1.01)	0.991	1.00 (0.90-1.12)	0.278	1.03 (0.99-1.07)	0.182
	Model 5b	1.21 (1.02-1.45)	**0.033**	0.99 (0.96-1.01)	0.989	1.00 (0.90-1.12)	0.302	1.03 (0.99-1.07)	0.198

Model 1: Unadjusted model. Model 2: adjusted by sex and Charlson Index. Model 3: Model 2 plus smoking status, systolic blood pressure, muscle/fat ratio and asymmetric dimethylarginine levels. Model 4: Model 3+ creatinine levels, polypharmacy and log (Homeostasis Model Assessment of Estimated Insulin Resistance). **Bold** values indicate the statistical significance of the associations.

FTS5 = Frailty Trait Scale-5; PWV = pulse wave velocity.

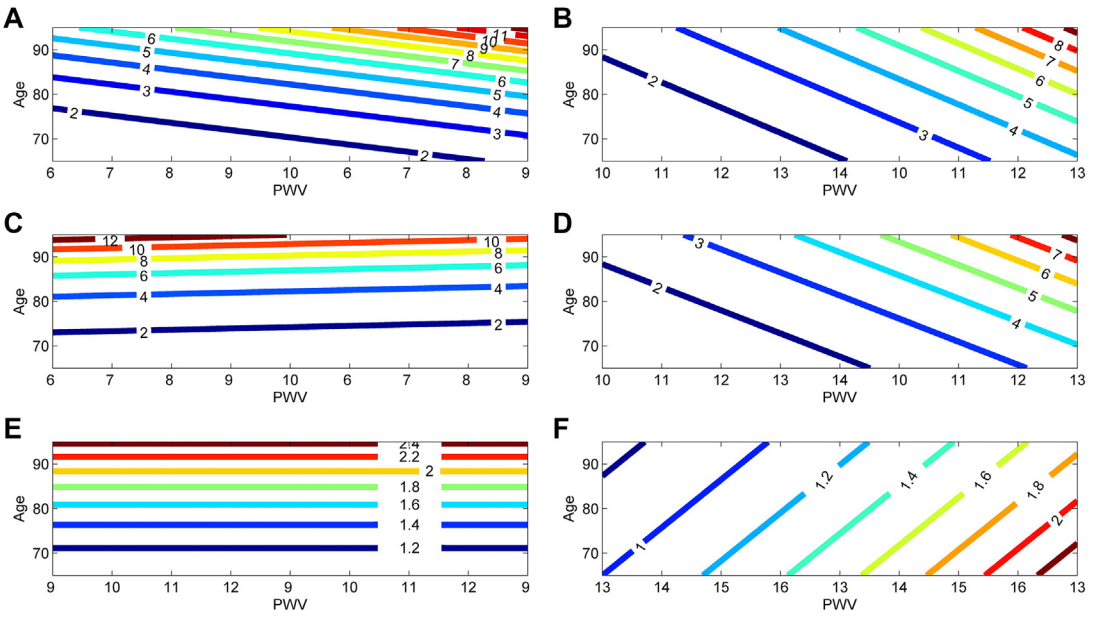
classical outcomes, mainly cardiovascular and cerebrovascular events [12-14].

Frailty was assessed using 2 instruments that have shown different characteristics inside the same conceptual framework (FP). The persistence of the findings disregarding the tool suggests consistency to our findings.[9,30,31]

Cardiovascular disease is expected to be the leading cause of morbidity and mortality in the coming years. Arterial stiffness has been closely associated with the aging process, independent of traditional cardiovascular risk factors.[26] Consistent evidence suggests that arterial stiffness is a subclinical, strong, and valid vascular biomarker for the quantification of atherosclerosis and severe cardiovascular dysfunction,[20,32] even in well-functioning older adults.[33] Increased arterial stiffness occurs mainly in central arteries, such as the aorta[34] or carotid artery, and it has been shown to be a risk factor that increases the risk of deterioration of mental capacities[18] and, according to our results, emerges as a risk factor that is independently associated to the outcomes, as it is shown in the multivariant models adjusting for comorbidities, other cardiovascular risk factors like smoking or insulin resistance and endothelial function.

Central blood pressure has been associated with a reduction in physical function[35,36] and performance as hand grip strength levels.[37,38] As it is well known, frailty is a multidomain expression of other underlying physiological mechanisms in the individual, and impairments on these domains, such as gait speed or grip strength, could be the tell-tale sign of dysfunction. The result will largely depend on the baseline status,[39] so early detection to prevent and revert these conditions could delay or modify them.[40,41] Vascular dysfunction is also known to be negatively associated with muscle outcomes such as muscle strength, muscle mass and muscle function.[42] Studies have shown that both macrovascular function

FIGURE 1 **ORs for the Risk of Incident Frailty and Worsening Disability Depending Upon Age and PWV**



(A) Incident frailty (frailty phenotype)—pulse wave velocity ≤10, **(B)** incident frailty (frailty phenotype)—pulse wave velocity >10, **(C)** incident frailty (Frailty Trait Scale-5)—pulse wave velocity ≤10, **(D)** incident frailty—(Frailty Trait Scale-5) pulse wave velocity >10, **(E)** worsening disability—pulse wave velocity ≤12.5, and **(F)** worsening disability >12.5. OR = odds ratio; PWV = pulse wave velocity.

(assessed by PWV and other measures) and microvascular function (eg, perfusion/microvascular flow into tissue and capillary density) can impact skeletal muscle outcomes. This lends insights into our findings on the association of PWV with frailty, disability, and even mortality, since low skeletal muscle mass and function plays a central role in incident frailty[43,44] and in mobility-disability,[45,46] and loss of skeletal muscle has been associated with mortality.[47] Poor vascular function can lead to a decrease in blood flow into the muscle, impacting the availability of nutrients need for muscle function[48,49] which will eventually leading to loss of muscle mass, strength, and function.[50] Kattainen et al[51] showed that over

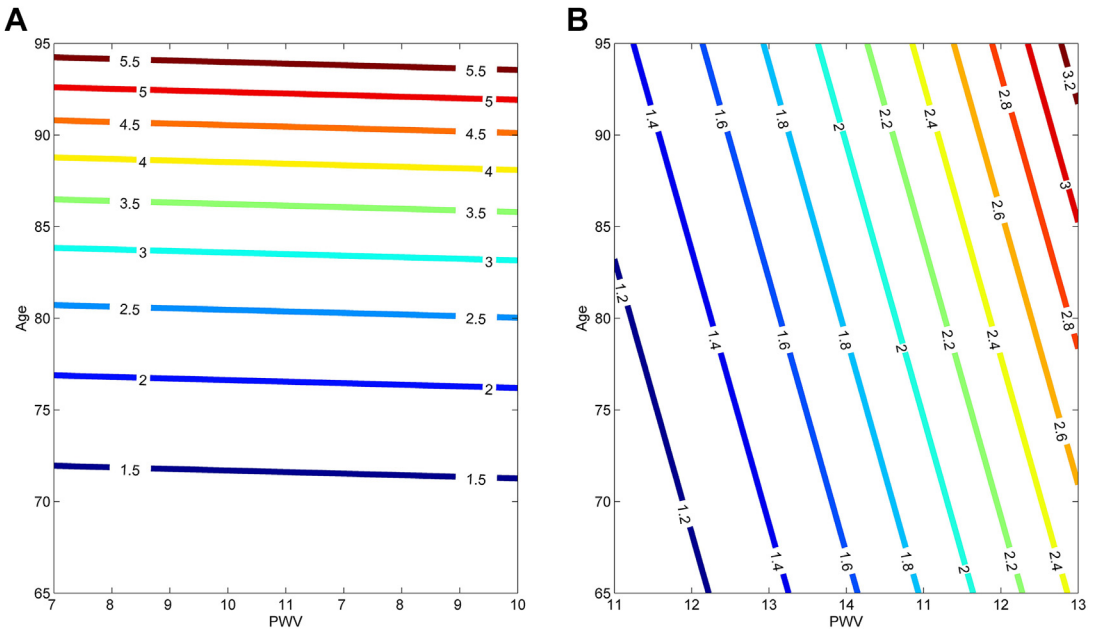
TABLE 4 **Hazard Regression Models Showing the Association Between PWV and Age With Mortality**

		PWV >11 m/s				PWV ≤11 m/s			
		PWV		Age		PWV		Age	
	Model	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Death									
	Model 1	1.37 (1.19-1.58)	**<0.001**	1.01 (0.98-1.03)	0.813	0.98 (0.85-1.14)	0.595	1.06 (1.02-1.11)	**0.003**
	Model 2	1.41 (1.21-1.63)	**<0.001**	1.01 (0.98-1.04)	0.616	0.96 (0.83-1.11)	0.536	1.07 (1.03-1.12)	**0.001**
	Model 3	1.41 (1.21-1.65)	**<0.001**	1.01 (0.98-1.04)	0.746	0.98 (0.84-1.13)	0.441	1.08 (1.03-1.12)	**0.001**
	Model 4	1.34 (1.15-1.57)	**<0.001**	1.01 (0.98-1.04)	0.870	1.01 (0.88-1.17)	0.523	1.06 (1.02-1.11)	**0.005**
	Model 5a	1.28 (1.09-1.50)	**0.003**	1.01 (0.98-1.04)	0.782	1.02 (0.88-1.18)	0.553	1.05 (1.01-1.10)	**0.019**
	Model 5b	1.33 (1.13-1.57)	**0.001**	1.01 (0.98-1.04)	0.444	1.06 (0.91-1.23)	0.454	1.06 (1.01-1.10)	**0.009**
	Model 6a	1.34 (1.14-1.56)	**<0.001**	1.01 (0.98-1.03)	0.638	1.04 (0.89-1.20)	0.631	1.05 (1.01-1.10)	**0.013**
	Model 6b	1.33 (1.13-1.55)	**<0.001**	1.01 (0.98-1.04)	0.470	1.03 (0.89-1.20)	0.655	1.06 (1.01-1.10)	**0.008**

Model 1: Unadjusted model. Model 2: adjusted by sex and Charlson Index. Model 3: Model 2 plus smoking status, systolic blood pressure, muscle/fat ratio and asymmetric dimethylarginine levels. Model 4: Model 3+ creatinine levels, polypharmacy and log (Homeostasis Model Assessment of Estimated Insulin Resistance). Model 5a: Model 4 + frailty status according to the Frailty Phenotype. Model 5 b: Model 4 + frailty status according to the Frailty Trait Scale 5. Model 6a: Model 4 + disabled according to Katz Index. Model 6 b: Model 4+ disabled according to Katz Index excluding incontinence item. **Bold** values indicate the statistical significance of the associations.

PWV = pulse wave velocity.

FIGURE 2 **HRs for the Risk of Death Depending Upon Age and PWV**



(A) Death—pulse wave velocity ≤11 m/s, **(B)** death—pulse wave velocity >11 m/s. PWV = pulse wave velocity.

25% of disability could be attributable to cardiovascular disease in older adults between 65 and 74 years. In women, older adults with an ankle-brachial index <0.6 had an increased risk of incident disability for walking performance tests (gait speed, number of city block walked last week, and ability to walk one-quarter of a mile), but not for other functional outcomes (ie, 5 times sit-to-stand test).[52]

The relationship between arterial stiffness and mortality has been determined previously.[17,21,53] According to our study, this association is independent of variables classically associated with mortality, such as cardiovascular disease, but also frailty and disability. Moreover, our findings reinforce the idea of a nonlinear association between the extent of vascular disease and the risk of adverse functional events.[54] Depending on the functional adverse event, a different threshold has been found, similarly to that described in the literature for classical outcomes. Regarding the threshold for mortality, our results are quite similar to those obtained by Sequí-Dominguez et al. They found in their systematic review and meta-analysis that the cut-off points for cardiovascular mortality and for all-cause mortality were 10.7 and 11.5 m/s, respectively.[17] In our work, a PWV >11 m/s was associated with mortality, mainly in cardiovascular origin. Other threshold (10 m/s) has been proposed by different entities to predict mortality regardless of age.[14,55] In our study this threshold was associated with incident frailty, but not with mortality, highlighting the relevance of the age of the cohort in the determination of that threshold. Finally, it must be established that these thresholds are usually higher in people with diabetes,[56] a population excluded in our study. These similarities between the thresholds for both cardiovascular death and incident frailty raise the hypothesis of a relationship between cardiovascular disease and frailty. This association has been explored and shown in other works, including some from our group.[10] However, its role in the association shown in the current study does not seem quite relevant, taking into account that this relationship was not significantly modified after adjusting for comorbidities, including CVD. Nevertheless, assessing the relationships between each cardiovascular outcome, frailty and PWV offers opportunities for further research.

In addition to supporting a longitudinal (ie, potentially causal), "dose-dependent," relationship between macrovascular disease and functional decline since its earliest (frailty) to advanced

(disability) stages, support the evaluation of PWV to identify those at the greatest risk of developing frailty or disability. Early assessment in individuals at risk can lead to early intervention with exercise and specialized nutrition,[57,58] improving vascular function and thus preventing functional decline.

The relationship between arterial stiffness and functional deterioration opens options for intervention. There are few studies assessing the effect of exercise interventions on arterial stiffness,[59,60] but they show benefit of physical exercise programs on arterial stiffness. In this same regard, similar evidence is available regarding nutritional interventions. Recently a randomized controlled trial using a combined intervention (diet and physical exercise) in older obese people have shown benefit on arterial stiffness.[61] Although they look promising, they have been generally carried out in populations younger than 70 years old, and they have not assessed if the improvement in arterial stiffness in frail people improved the condition. Thus, both confirming and expanding the results in older populations, frail and/or disabled, are needed.

STRENGTHS. Our study presents several strengths including assessment of a relatively large population which allows the adverse events ascertainment including and accounting for multiple confounders in the statistical analysis. Another strength is the transversal and longitudinal design. Moreover, arterial stiffness is evaluated according to PWV measurement, a noninvasive, simple, and useful tool, which is considered the gold standard. Frailty was evaluated according to the FP, one of the most used frailty tools and the FTS5. The similarity of our findings regardless of the frailty tool used reinforced our results.

STUDY LIMITATIONS. Although PWV is considered the gold standard method to assess arterial stiffness, it has not traditionally been used in clinical settings for community cohorts.[62] We did not include patients with diabetes mellitus in this study; however, there is a strong association between diabetes mellitus with both frailty/disability (outcomes) and atherosclerosis (predicting variable), and in the progression toward disability and death.[63] Thus, our findings may not extent to this population or others not represented in TSHA. Finally, excluding to those with missing data could induce some bias in our findings, but we do feel that this is unlikely, taking into account that the characteristics of those excluded are not different from those included to the analysis.

CONCLUSIONS

Arterial stiffness is a significant factor associated to the development of functional impairments and mortality. PWV thresholds differ based on the outcome of interest. Assessing arterial stiffness provides relevant information that may be useful for targeting interventions with the aim of avoiding adverse events and promoting well-being in older adults living in the community.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Arterial stiffness is one of the major determinants of adverse events in nondiabetic community-dwelling older adults.

TRANSLATIONAL OUTLOOK: Assessment and detection of arterial stiffness could allow the identification of older adults at increased risk of developing adverse events, even in those that are high functioning.

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KEY WORDS disability, frailty, mortality, older adults, pulse wave velocity (PWV)

APPENDIX For supplemental tables and figures, please see the online version of this paper.