

JYX



This is a self-archived version of an original article. This version may differ from the original in pagination and typographic details.

Author(s): Hinrichs, Timo; Portegijs, Erja; Rantanen, Taina; Infanger, Denis; Schmidt-Trucksäss, Arno; Karavirta, Laura

Title: Association between arterial stiffness and walking capacity in older adults

Year: 2022

Version: Published version

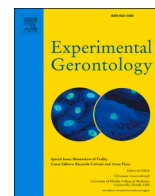
Copyright: © 2022 The Authors. Published by Elsevier Inc.

Rights: CC BY 4.0

Rights url: <https://creativecommons.org/licenses/by/4.0/>

Please cite the original version:

Hinrichs, T., Portegijs, E., Rantanen, T., Infanger, D., Schmidt-Trucksäss, A., & Karavirta, L. (2022). Association between arterial stiffness and walking capacity in older adults. *Experimental Gerontology*, 167, Article 111925. <https://doi.org/10.1016/j.exger.2022.111925>



Association between arterial stiffness and walking capacity in older adults

Timo Hinrichs^{a,*}, Erja Portegijs^c, Taina Rantanen^b, Denis Infanger^a, Arno Schmidt-Trucksäss^a, Laura Karavirta^b

^a Division of Sports and Exercise Medicine, Department of Sport, Exercise and Health, University of Basel, Basel, Switzerland

^b Faculty of Sport and Health Sciences and Gerontology Research Center, University of Jyväskylä, Jyväskylä, Finland

^c University of Groningen, University Medical Center Groningen, Center for Human Movement Sciences, Groningen, the Netherlands

ARTICLE INFO

Section Editor: Christiaan Leeuwenburgh

Keywords:

Octogenarian
Vascular stiffness
Pulse wave analysis
Walking
Mobility limitation
Population-based

ABSTRACT

Background and aim: Arterial stiffening – a process that is largely due to intimal thickening, collagen disposition or elastin fragmentation – significantly contributes to cardiovascular events and mortality. There is also some evidence that it may negatively affect physical function. This study aimed to evaluate whether arterial stiffness was associated with measures of walking capacity in a large, population-based sample of highly aged older adults.

Methods: A population-based sample of 910 community-dwelling adults (aged 75, 80, or 85 years) were investigated in a cross-sectional observational study. Pulse wave velocity (PWV), a surrogate marker of arterial stiffness, was estimated based on the oscillometric recording of pulse waves at the brachial artery site. Walking capacity was assessed by 10-meter habitual walking speed, 10-meter maximum walking speed, and six-minute walk distance. We used multiple linear regression models to examine possible associations between PWV and parameters of walking capacity, and we adjusted the models for sex, age, socioeconomic status, anthropometry, physician-diagnosed diseases, prescription medication, smoking history, physical activity, and mean arterial pressure. Continuous variables were modelled using restricted cubic splines to account for potential nonlinear associations.

Results: Mean (standard deviation) 10-meter habitual walking speed, 10-meter maximum walking speed, and six-minute walk distance were 1.3 (0.2) m/s, 1.7 (0.4) m/s, and 413 (85) m, respectively. The fully adjusted regression models revealed no evidence for associations between PWV and parameters of walking capacity (all p-values >0.05).

Conclusion: Our results did not confirm previous findings suggesting a potential negative association between arterial stiffness and walking capacity in old age. Longitudinal studies, potentially taking additional confounders into account, are needed to disentangle the complex relationship between the two factors.

1. Background

Even in healthy individuals and in the absence of atherosclerotic disease, central elastic arteries are stiffening with increasing age (Kucharska-Newton et al., 2019; Vlachopoulos et al., 2015), a process that is largely due to intimal thickening, collagen deposition, or elastin fragmentation (Nagai et al., 1999; Virmani et al., 1991; Zieman et al., 2005). Arterial stiffening leads to a rise in systolic blood pressure and pulse pressure (Dart and Kingwell, 2001; Franklin et al., 1997), and it significantly contributes to cardiovascular events and mortality (Sutton-

Tyrrell et al., 2005; Vlachopoulos et al., 2010). Besides these frequently shown associations, there is also some evidence that arterial stiffening may be negatively associated with physical function, including walking capacity (Brunner et al., 2011; Dvoretzkiy et al., 2020; Watson et al., 2011).

Arterial stiffening has a number of negative pathophysiological consequences. These do not only refer to cardiac function, such as, e.g., increased left ventricular afterload, reduced coronary perfusion, increased myocardial work and myocardial deformation (Hwang et al., 2012; Lantelme et al., 2008), but also to the peripheral circulation.

* Corresponding author at: Division of Sports and Exercise Medicine, Department of Sport, Exercise and Health, University of Basel, Grosse Allee 6, 4052 Basel, Switzerland.

E-mail address: timo.hinrichs@unibas.ch (T. Hinrichs).

URL: <https://mobility.dsb.unibas.ch/en/> (T. Hinrichs).

<https://doi.org/10.1016/j.exger.2022.111925>

Received 23 June 2022; Received in revised form 8 July 2022; Accepted 8 August 2022

Available online 10 August 2022

0531-5565/© 2022 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Arterial stiffening impairs the unique ability of the cardiovascular system to convert the marked pulsatile central blood flow into a smooth pattern that minimizes the dynamic stress on the smaller peripheral vessels (Mitchell, 2008; O'Rourke et al., 1984). In consequence, arterial stiffening may negatively affect the skeletal muscle microcirculation and thereby, potentially, skeletal muscle function (Payne and Bearden, 2006).

The clinical measure of pulse wave velocity (PWV) is widely used to operationalize arterial stiffness (Kohn et al., 2015). It is an estimate of the speed of the pressure wave traveling along the aortic and aorto-iliac pathway (Nemcsik et al., 2017), and thereby an indirect, surrogate measure of arterial stiffness – with higher PWV values indicating increased stiffness. While originally, PWV was measured invasively, a number of non-invasive methods have evolved over the past decades, including systems that derive PWV from a recording of pressure waveforms at the carotid and femoral artery using electrocardiography for synchronization, and – more lately – cuff-based systems that calculate aortic PWV based on the oscillometric recording of pulse waves at the brachial artery only (Townsend et al., 2015). Brachial cuff-based systems showed good validity in comparison to carotid-femoral measurements and they have the potential to facilitate PWV measurements in everyday clinical practice settings (Hametner and Wassertheurer, 2017; Nürnberger et al., 2011; Wassertheurer et al., 2010).

In older adults, measures of walking capacity have been shown to be predictive of falls (van Kan et al., 2009), hospitalisation (Cesari et al., 2005), and mortality (Cesari et al., 2005; Studenski et al., 2011). Deficits in walking capacity are associated with social isolation (Bevilacqua et al., 2021), anxiety and depression (Vink et al., 2008), and a reduced quality of life (Netuveli et al., 2006). Furthermore, the ability of older adults to maintain their independence and to stay in their own homes largely depends on their walking capacity (Reuben et al., 2004; von Bonsdorff et al., 2006). The research into correlates of walking capacity in old age may lead to novel approaches and treatment options to impede the age-related functional decline.

Studies on the relationship between PWV and walking capacity in old age are still scarce (Dvoretzkiy et al., 2020). The Whitehall II study found a significant inverse association between PWV and habitual walking speed in middle aged to older adults, independent of various health conditions (Brunner et al., 2011). This was partly contradicted by the Health, Aging and Body Composition (Health ABC) Study which found an independent inverse association in older adults (aged 70 to 79 years) with peripheral arterial disease but not in those without the disease (Watson et al., 2011). Recently, Ogawa et al. (2020) demonstrated a significantly lower brachial-ankle PWV in those within the highest walking speed-tertile compared to those within the lowest walking speed-tertile in a sample of community-dwelling older adults (aged 65+). While the aforementioned studies used short-distance walking tests only, Gonzales (2013) used a 400 meter walk test and derived mean walking speed as well as distance walked within the first 2 min in a small sample of 21 older adults. A partial correlation analysis (adjusting for selected potential confounders) revealed a significant negative correlation between PWV and walking speed as well as distance. In summary, findings of existing studies on the relationship between PWV and walking capacity are inconsistent and limitations still include a scarcity of data on older adults aged 75+ and a limited selection of measures of walking capacity per study. Statistically, existing studies did not take the potential non-linearity of the relationship into account.

The present study aimed to evaluate if PWV (measured by a brachial cuff-based device) is associated with three different measures of walking capacity (10-meter habitual as well as maximum walking speed, and six-minute walk distance) in a large, population-based sample of older adults aged 75, 80, and 85 years. Measures that were taken into account when analyzing the potential associations between measures of PWV and walking capacity included sociodemographic and -economic factors, anthropometry, presence of chronic disease (cardiac disease,

cerebral or cerebrovascular disease, diabetes, vascular disease), beta-blocker intake, antihypertensive medication, smoking history, habitual physical activity, and mean arterial pressure. In order to account for potential nonlinear associations, all continuous variables were modelled using restricted cubic splines (Harrell, 2015).

2. Methods

2.1. Study design

AGNES (“Active Ageing – Resilience and External Support as Modifiers of the Disablement Process”) was an observational study of three age cohorts (75, 80, and 85 years) with 1021 participants (for sample size and power calculations please refer to the published study protocol) (Rantanen et al., 2018). Its cross-sectional data collection (September 2017 to December 2018) included phone and face-to-face interviews in people's homes, postal questionnaires, and assessments in the research center. AGNES was approved by the ethical committee of the Central Finland Health Care District (23 August 2017).

2.2. Target group, inclusion and exclusion

The study targeted adults aged 75, 80 and 85 living in postal areas within a 10 kilometer radius of the city center or within reach of local public transportation of the city of Jyväskylä, Finland. Inclusion criteria were: being aged 75, 80 or 85 years, living independently in the recruitment area, and providing written informed consent. Only those who were unwilling to participate or unable to communicate were excluded.

2.3. Recruitment and participants

Participants were recruited from the Digital and Population Data Services Agency in Finland. Invitations were sent to 2791 people, 2348 were interviewed on the phone about their willingness to participate, baseline postal questionnaire and/or home interviews were completed by 1021 participants. Of these 1021 participants, 910 volunteered to take part in laboratory assessments at the research center. Those who participated in the laboratory assessments had a lower median age (78.5 vs. 79 years) and a higher self-rated health (47.4 vs. 30.2 % with good or very good health), and they were more frequently male (43.1 vs. 39.6 %) compared to those who only filled in the postal questionnaire and/or took part in the home interviews (for details on the recruitment process please see Portegijs et al. (2019)). Arterial stiffness measurements as well as the assessments of walking capacity were exclusively conducted at the research center; we therefore limited our analyses to these participants.

2.4. Main measures

All assessments of arterial stiffness and physical function were performed at the research center by trained assessors. For details on all measurement procedures, please refer to the published study protocol (Rantanen et al., 2018).

2.4.1. Walking capacity (outcome)

Habitual as well as maximum walking speed were assessed over a 10-meter distance using a light barrier system. Walking started five meters before the first light barrier (to allow for acceleration) and stopped well past the finish line (in order to avoid deceleration within the 10-meter distance). Participants performed two walks: 1) with the instruction to walk at their habitual speed, i.e., the speed they would use when going for errands; 2) with the instruction to walk as fast as possible, without compromising safety (Sakari-Rantala et al., 1998). During both walks, participants were allowed to use a walking aid, if needed.

Furthermore, participants performed a self-paced six-minute walk

test (Holland et al., 2014; Simonsick et al., 2014). For safety reasons and in order to facilitate continuous walking performance over the entire test duration, participants were asked to walk at usual walking speed rather than maximal speed (Gremeaux et al., 2008). Participants were allowed to use a walking aid, if needed. Tests were performed on an indoor corridor with 40-meter lap length. The total distance walked within 6 min was measured.

2.4.2. Arterial stiffness (main independent measure)

Arterial stiffness was measured by a non-invasive cuff-based device (Diagnostic Station DS20, Schiller AG, Baar, Switzerland) that captures brachial blood pressure and pulse wave forms allowing to estimate the central aortic hemodynamics and PWV. Measurements were performed in a seated position (back resting against the chair backrest, feet flat on the floor, and legs uncrossed) after resting for at least 10 min to ensure hemodynamic stability. Participants were instructed to refrain from talking during the test. Each measurement started with a recording of brachial blood pressure followed by a pulse wave recording with the cuff inflated at the diastolic blood pressure level. Ten stable consecutive pulses were filtered and averaged by the device to calculate the central aortic pulse wave. Aortic pulse waves were calculated via a general transfer function, based on the modification of a certain frequency range in the recorded peripheral pressure waves (Wassertheurer et al., 2010; Wassertheurer et al., 2008). Based on these calculations, the central PWV was estimated (Endes et al., 2015; Nunan et al., 2012). A measurement was considered as being “valid” if >50 % of recorded pulse waves were usable for the estimation of PWV. Three measurements (with 1 min of rest in-between) were performed. In case of three valid measurements, the mean value of the second and third measurement was used for analysis; only if the difference between the second and third measurement was ≥ 0.5 m/s, the first measurement was taken into account and the mean value of the two closest measurements was used for analysis. In case of two valid measurements, the mean of these two measurements was used for analysis. In case of only 1 valid measurement, a “missing value” was assigned to the respective participant (Brunner et al., 2011; Endes et al., 2015; Reshetnik et al., 2017).

2.5. Further measures

Age and sex were obtained from the Digital and Population Data Services Agency in Finland in the context of the recruitment. Body height and waist circumference (mean of three subsequent measurements) were measured by an assessor. Socioeconomic status (perceived financial situation and years of education), smoking history, physician-diagnosed diseases (cardiac disease, cerebral or cerebrovascular disease, diabetes, and vascular disease) and prescription medication (beta-blocker and antihypertensive medication) were assessed by self-report (Rantanen et al., 2018). Habitual physical activity was assessed by the Yale Physical Activity Survey for older adults (YPAS), the total score was calculated (DiPietro et al., 1993). Mean arterial pressure was derived from the arterial stiffness measurements.

2.6. Statistical analyses

All measures were analyzed descriptively (numbers, percentages, means, medians and standard deviations as appropriate). Outcomes of walking capacity (10-meter habitual walking speed, 10-meter maximum walking speed, and six-minute walk distance) were analyzed by sex and age group. We additionally performed two-way analyses of variance (ANOVAs) with PWV and parameters of walking capacity as outcomes and age group, sex and their interaction as independent variables. We used multiple linear regression models to examine possible associations between PWV and the three outcomes of walking capacity. Besides PWV, sex, age group, self-rated economic situation, years of education, body height, waist circumference, presence of chronic disease (cardiac disease, cerebral or cerebrovascular disease, diabetes, vascular disease),

beta-blocker intake, antihypertensive medication (other than beta-blocker), mean arterial blood pressure, smoking history, and physical activity were used as independent variables (potential confounders) using a stepwise approach (for details see Table 4). All continuous confounders were modelled using restricted cubic splines (i.e. “natural” splines) with four knots placed at specific percentiles of the variables to account for potential nonlinear associations (Harrell, 2015). Additionally, we assessed the evidence for a nonlinear relationship between PWV and the outcomes in the fully adjusted models. Specifically, we compared three models sequentially using likelihood ratio tests: 1) a model excluding PWV (the null model), 2) a model with PWV included linearly and 3) a model with PWV included as a spline as described above. Model fits were checked using diagnostic residual plots. Because there was little evidence for a nonlinear relationship between PWV and all three outcomes, we present the models where PWV was included linearly. We handled missing data using multiple imputation (Jakobsen et al., 2017; van Buuren, 2018). We imputed 50 datasets using predictive mean matching where all variables listed above served as predictors. Complete case analyses of the fully adjusted models were performed as sensitivity analyses. The fraction of missing observations for the outcomes 10-meter habitual walking speed, 10-meter maximum walking speed, and six-minute walk distance in the complete-case regression models were 12.4 %, 12.4 % and 15.1 %. All tests were two-sided, and the level of significance was set at 0.05.

3. Results

Participants (N = 910) had a median (interquartile range) age of 78.5 (75–80) years (Table 1). Descriptive analyses showed higher mean PWV values in older compared to younger age groups and higher mean values

Table 1
Participant characteristics (N = 910).

Characteristic	N	Category	%	Mean	SD	Median
Sex	910	Female	56.9			
Age group	910	74–75 years	47.7			
		78–80 years	32.1			
		83–85 years	20.2			
Body height (cm)	910			164.2	8.9	163.5
Waist circumference (cm)	907			96.7	12.6	97
Perceived financial situation	904	Very poor	0			
		Poor	1.8			
		Fair	37.6			
		Good	50.0			
		Excellent	10.4			
Education (years)	900	Cannot say	0.2	11.6	4.2	11
Smoking history (daily or almost daily for ≥ 1 year)	893	No	70.3			
		Yes, quit smoking	27.2			
		Yes, still smoking	2.5			
Physical activity (YPAS score points)	891			56.4	23.3	54
Cardiac disease	908	Yes	38.5			
Cerebral or cerebrovascular disease	905	Yes	7.7			
Diabetes	908	Yes	17.0			
Vascular disease	907	Yes	54.1			
Beta-blocker	904	Yes	37.8			
Hypertensive medication (other than beta-blocker)	904	Yes	56.4			
Mean arterial pressure (mm Hg)	857			112.7	16.4	111.5

SD – standard deviation; YPAS – Yale Physical Activity Survey for older adults.

Table 2
Descriptive analyses of pulse wave velocity and parameters of walking capacity by sex and age group.

Parameter	Sex	Age group	N	Mean	SD	Median
Pulse wave velocity (m/s)	Male	74–75	178	11.61	0.63	11.55
		78–80	128	12.37	0.63	12.35
		83–85	74	13.30	0.72	13.29
		Total	380	12.19	0.91	12.12
	Female	74–75	236	11.74	0.69	11.67
		78–80	145	12.77	0.72	12.85
		83–85	96	13.64	0.80	13.60
		Total	477	12.43	1.04	12.31
		Total	857	12.33	0.99	12.24
Habitual 10-meter walking speed (m/s)	Male	74–75	181	1.34	0.24	1.36
		78–80	132	1.26	0.24	1.27
		83–85	75	1.15	0.27	1.17
		Total	388	1.28	0.25	1.29
	Female	74–75	250	1.31	0.23	1.32
		78–80	158	1.21	0.22	1.22
		83–85	103	1.11	0.21	1.12
		Total	511	1.24	0.23	1.25
		Total	899	1.26	0.24	1.27
Maximum 10-meter walking speed (m/s)	Male	74–75	180	1.99	0.41	2.00
		78–80	132	1.84	0.43	1.84
		83–85	75	1.61	0.43	1.66
		Total	387	1.86	0.44	1.87
	Female	74–75	249	1.76	0.33	1.77
		78–80	158	1.59	0.33	1.64
		83–85	102	1.44	0.37	1.41
		Total	509	1.64	0.36	1.67
		Total	896	1.74	0.41	1.76
Six-minute walk distance (m)	Male	74–75	176	453.3	79.1	458.5
		78–80	126	420.3	80.4	420.5
		83–85	70	386.1	87.8	393.5
		Total	372	429.5	84.9	435.0
	Female	74–75	244	427.8	76.3	432.0
		78–80	152	390.6	76.4	388.0
		83–85	96	346.7	81.1	344.5
		Total	492	400.5	83.2	405.0
		Total	864	413.0	85.1	418.5

SD – standard deviation.

in women compared to men. Men had a faster walking speed and a farther 6-minute walk distance than women; walking speed and walk distance were slower and shorter respectively in older compared to younger age groups (Tables 2 and 3). Eighty-seven percent of the total sample had a habitual 10-meter walking speed of 1.0 m/s or higher. In the regression analyses adjusted for all independent variables, no significant association was found between PWV and the parameters of walking capacity (Table 4, model 4). Coefficients were close to zero for all three outcomes. The lower and upper bound of a confidence interval define the most plausible or compatible range for the population parameter based on the data and the model at some specific confidence

Table 3
Results of two-way analyses of variance (ANOVAs) with PWV and parameters of walking capacity as outcomes and age group, sex and their interaction as independent variables.

Outcome	Effect	Degrees of freedom	F-value	p
Pulse wave velocity (m/s)	Main effect age group	2, 851	442.19	<0.001
	Main effect sex	1, 851	29.67	<0.001
	Interaction	2, 851	3.46	0.032
Habitual 10-meter walking speed (m/s)	Main effect age group	2, 893	48.89	<0.001
	Main effect sex	1, 893	5.49	0.019
	Interaction	2, 893	0.13	0.877
Maximum 10-meter walking speed (m/s)	Main effect age group	2, 890	54.44	<0.001
	Main effect sex	1, 890	78.65	<0.001
	Interaction	2, 890	0.57	0.568
Six-minute walk distance (m)	Main effect age group	2, 858	56.97	<0.001
	Main effect sex	1, 858	29.57	<0.001
	Interaction	2, 858	0.45	0.636

p-values ≤0.05 are bolded.

Table 4
Association of pulse wave velocity with parameters of walking capacity (N = 910, imputed dataset).

Outcome	Pulse wave velocity (m/s) (independent measure)			
	Model ^a	Coefficient	95 % CI	p
Habitual 10-meter walking speed (m/s)	1	0.04	0.01 to 0.06	0.003
	2	0.04	0.01 to 0.06	0.001
	3	0.02	−0.03 to 0.06	0.514
	4	0.01	−0.03 to 0.06	0.568
Maximum 10-meter walking speed (m/s)	1	0.05	0.02 to 0.09	0.004
	2	0.05	0.02 to 0.09	0.002
	3	−0.01	−0.09 to 0.07	0.817
	4	−0.01	−0.08 to 0.06	0.752
Six-minute walk distance (m)	1	12.6	3.8 to 21.5	0.005
	2	12.9	4.6 to 21.2	0.002
	3	4.1	−12.8 to 21.0	0.634
	4	2.6	−13.2 to 18.3	0.749

^a Regression model 1 was adjusted for sociodemographic factors (sex, age group, economic situation, and education); model 2 was adjusted for socio-demographic and anthropometric factors (body height and waist circumference); model 3 was adjusted for sociodemographic, anthropometric and health-related factors (cerebral or cerebrovascular disease, cardiac disease, vascular disease, diabetes, beta-blocker, antihypertensive medication, and mean arterial pressure); and model 4 was adjusted for sociodemographic, anthropometric, health-related, and behavioral factors (physical activity and smoking history).

level (Infanger and Schmidt-Trucksäss, 2019). Our data were compatible with a 0.03 m/s slower as well as a 0.06 m/s faster habitual walking speed; a 0.08 m/s slower as well as a 0.06 m/s faster maximum walking speed; and a 13.2 m shorter as well as a 18.3 m farther 6-minute walk distance per additional m/s in PWV; as indicated by the lower and upper bounds of the 95 % confidence intervals. Values are below the cutoffs that are usually regarded as “substantial meaningful change” (0.1 m/s for changes in walking speed and 50 m for changes in 6-minute walk distance (Perera et al., 2006)). Results of the complete case analyses were not markedly different from the results of the analyses using the imputed dataset.

4. Discussion

We investigated a large, population-based sample of community-dwelling older adults aged 75, 80, and 85 years and did not find evidence for an association between PWV and three different parameters of walking capacity.

Our analyses showed an age-related decline of habitual and maximum walking speed and better walking capacity in men compared to women. This is in line with findings of large observational studies and meta-analyses (Bohannon and Williams Andrews, 2011; Cazzoletti et al., 2022; Kasovic et al., 2021). As expected, we found an age-related

increase of PWV. This relationship is well-known from the literature (Brunner et al., 2011; Mattace-Raso et al., 2010). PWV values were higher in women compared to men. This is in line with findings of the Berlin Aging Study II (N = 1100; mean age 75.6, SD 3.8 years) which applied a similar method to determine PWV and found slightly higher (mean difference 0.02 m/s, $p = 0.006$) PWV values in women (Pohrt et al., 2022). The Reference Values for Arterial Stiffness Collaboration (Mattace-Raso et al., 2010) reported a “negligible influence of gender on PWV” with higher values in males (difference of <0.1 m/s; $p = 0.04$) based on their analysis of data from 16867 individuals (mean age 55, SD 17; range 15 to 97 years) from eight European countries.

There have been a number of cross-sectional studies suggesting that there might be an inverse relationship between PWV and parameters of walking capacity in older adults. Brunner et al. (2011) investigated carotid-femoral PWV and usual walking speed over an 8-foot walking course in a large sample (N = 5286) of adults aged 55 to 78 years. The regression analysis (adjusted for several potential confounders including age, sex, mean arterial pressure, chronic disease and antihypertensive treatment) revealed a significant negative association between PWV (m/s) and walking speed (m/s) (coefficient -0.67 ; 95 % confidence interval -1.06 to -0.24). Ogawa et al. (2020) investigated 492 older adults between 65 and 96 years of age. In a multivariable regression analysis (adjusted for a high number of potential confounder including age, sex, body mass index, mean arterial pressure, smoking status, exercise status, and anti-hypertensive medication), higher brachial-ankle PWV (cm/s) was significantly associated to a lower maximum 6-meter walking speed (m/s) (coefficient -0.088 ; $p = 0.032$). Gonzales (2013) investigated a small (N = 21) sample of older adults aged 61 to 78. Participants performed a 400 meter walk test; mean walking speed of the whole test as well as distance walked within the first 2 min were derived. After adjustment for age, body mass index, waist circumference and systolic blood pressure, higher carotid-femoral PWV was negatively correlated to walking speed ($r = -0.48$; $p < 0.05$) and to 2-minute walk distance ($r = -0.51$; $p < 0.05$).

Our findings are in line with those of Watson et al. (2011) in the Health ABC cohort study. They measured carotid-femoral PWV at baseline and usual walking speed on a straight 20-meter course over seven years in a large sample of older adults (N = 2172) initially aged 70 to 79 years. No significant association between PWV (standard deviations) and longitudinal walking speed (m/s) (coefficient -0.005 ; 95 % confidence interval -0.012 to 0.002) was found by mixed-effects models (adjusted for several potential confounders including age, sex, body mass index, systolic blood pressure, heart rate, smoking, physical activity, coronary heart disease, diabetes and hypertension) in the full cohort. However, they identified a statistically significant negative relationship between PWV (standard deviations) and walking speed (m/s) in the subgroup of participants affected by peripheral arterial disease (defined by an ankle-brachial index of <0.9 ; coefficient -0.028 ; 95 % confidence interval -0.047 to 0.010). Authors argued that central (carotid-femoral) arterial stiffness may be especially detrimental to walking capacity in those individuals who already have a compromised function of peripheral arteries. Comparably to our sample, the Health ABC cohort initially had a rather high mobility status with only 7 % having a walking speed of lower than 1.0 m/s.

Our findings are limited by the cross-sectional design including the inability to infer causality. Even though the AGNES study is population-based, the high age of our sample in combination with a relatively high burden of participating in the assessments at the study center (typically lasting about 3 h) probably led to a selection of healthier and more mobile older adults (Portegijs et al., 2019). We used three different tests of walking capacity, including a longer duration walking test, which presumably increases the sensitivity to capture small differences in walking capacity among well-functioning older adults (Sayers et al., 2006). However, for safety reasons, we asked participants to walk at usual instead of maximum walking speed during the six-minute walk test. Therefore, in our sample of rather well-functioning older

participants, demands of the test might not have been high enough to render arterial stiffness and possibly insufficient leg perfusion during muscle contraction a performance-limiting factor.

While most previous studies on PWV and walking capacity used tonometry-based methods to estimate carotid-femoral PWV (Brunner et al., 2011; Gonzales, 2013; Watson et al., 2011), we applied an oscillometric method that uses pulse waves assessed at the brachial artery site only. A good agreement between methods has been demonstrated (Wassertheurer et al., 2010; Weber et al., 2011). However, both, tonometry-based as well as oscillometric measurements, only provide an estimate of the hemodynamics of central arteries, even though PWV is known to markedly vary along the complete arterial tree due to variations in arterial structure and geometry (Latham et al., 1985; Nichols and McDonald, 1972; Segers et al., 2009; Sugawara et al., 2010). Thereby local mechanical properties of peripheral arteries might be neglected which may have separate relationships with walking capacity in older adults (Gonzales, 2013). In support of this hypothesis, Gonzales et al. (2015) found that, after a fast-pace 400 meter walk test, older adults who felt more tired had a higher local stiffness of the superficial femoral artery but not of the carotid artery, than their counterparts who reported feeling more energetic after the test.

Strengths of the present study include the population-based approach and the large sample of highly aged individuals. In our analyses, we took the potential non-linearity of the relationship and a large number of potential confounders into account. Existing studies used quite comparable sets of potential confounders for adjusting their regression analyses (see above); future studies might choose to additionally measure and adjust for markers of chronic inflammatory processes that may affect both, arterial stiffness and walking capacity (Cesari et al., 2004; Marzetti et al., 2014; Yoon et al., 2020).

5. Conclusion

Our results did not confirm previous findings of cross-sectional studies suggesting a potential negative association between arterial stiffness and walking performance. Longitudinal studies are needed to disentangle the complex relationship between the two factors.

CRedit authorship contribution statement

Timo Hinrichs: funding acquisition, conceptualization, methodology, data curation, writing – original draft. **Erja Portegijs:** conceptualization, methodology, project administration, supervision, investigation, data curation, writing – review & editing. **Taina Rantanen:** funding acquisition, conceptualization, methodology, project administration, supervision, writing – review & editing. **Denis Infanger:** conceptualization, methodology, formal analysis, writing – review & editing. **Arno Schmidt Trucksäss:** conceptualization, methodology, writing – review & editing. **Laura Karavirta:** funding acquisition, conceptualization, methodology, project administration, supervision, investigation, data curation, writing – review & editing.

Declaration of competing interest

None of the authors have any conflicts of interest with any entity with regard to this study.

Acknowledgements

In the years 2016 to 2021, the AGNES project has been financially supported by grants of the European Research Council (grant number 693045 to TR and grant numbers 339391 and 346462 to LK) and the Academy of Finland (grant number 310526 to TR). A nested project on arterial stiffness and physical function has received additional support by Sport & Exercise Medicine Switzerland (SEMS Research Prize 2021 to TH).

The devices used for the arterial stiffness measurements have been provided by the Schiller AG, Baar, Switzerland. After the measurement period, devices have been returned to the company. The Schiller AG has no role in study design, study conduct, data analyses, interpretation of findings, or decision to publish findings.

References

- Bevilacqua, G., Jameson, K.A., Zhang, J., Bloom, I., Ward, K.A., Cooper, C., Dennison, E. M., 2021. The association between social isolation and musculoskeletal health in older community-dwelling adults: findings from the hertfordshire cohort study. *Qual. Life Res.* 30, 1913–1924.
- Bohannon, R.W., Williams Andrews, A., 2011. Normal walking speed: a descriptive meta-analysis. *Physiotherapy* 97, 182–189.
- Brunner, E.J., Shipley, M.J., Witte, D.R., Singh-Manoux, A., Britton, A.R., Tabak, A.G., McEniery, C.M., Wilkinson, I.B., Kivimaki, M., 2011. Arterial stiffness, physical function, and functional limitation: the Whitehall II Study. *Hypertension* 57, 1003–1009.
- Cazzolletti, L., Zanolin, M.E., Dorelli, G., Ferrari, P., Dalle Carbonare, L.G., Crisafulli, E., Alemayohu, M.A., Olivieri, M., Verlato, G., Ferrari, M., 2022. Six-minute walk distance in healthy subjects: reference standards from a general population sample. *Respir. Res.* 23, 83.
- Cesari, M., Kritchevsky, S.B., Penninx, B.W., Nicklas, B.J., Simonsick, E.M., Newman, A. B., Tyllavsky, F.A., Brach, J.S., Satterfield, S., Bauer, D.C., Visser, M., Rubin, S.M., Harris, T.B., Pahor, M., 2005. Prognostic value of usual gait speed in well-functioning older people—results from the health, aging and body composition study. *J. Am. Geriatr. Soc.* 53, 1675–1680.
- Cesari, M., Penninx, B.W., Pahor, M., Lauretani, F., Corsi, A.M., Rhys Williams, G., Guralnik, J.M., Ferrucci, L., 2004. Inflammatory markers and physical performance in older persons: the InCHIANTI study. *J. Gerontol. A Biol. Sci. Med. Sci.* 59, 242–248.
- Dart, A.M., Kingwell, B.A., 2001. Pulse pressure - a review of mechanisms and clinical relevance. *J. Am. Coll. Cardiol.* 37, 975–984.
- DiPietro, L., Caspersen, C.J., Ostfeld, A.M., Nadel, E.R., 1993. A survey for assessing physical activity among older adults. *Med. Sci. Sports Exerc.* 25, 628–642.
- Dvoretzkiy, S., Lieblein-Boff, J.C., Jonnalagadda, S., Atherton, P.J., Phillips, B.E., Pereira, S.L., 2020. Exploring the association between vascular dysfunction and skeletal muscle mass, strength and function in healthy adults: a systematic review. *Nutrients* 12, 715.
- Endes, S., Bachler, M., Li, Y.L., Mayer, C., Hanssen, H., Hametner, B., Schmidt-Trucksäss, A., Wassertheurer, S., 2015. Feasibility of oscillometric aortic pressure and stiffness assessment using the VaSera VS-1500: comparison with a common tonometric method. *Blood Press. Monit.* 20, 273–279.
- Franklin, S.S., Gustin, W.t., Wong, N.D., Larson, M.G., Weber, M.A., Kannel, W.B., Levy, D., 1997. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation* 96, 308–315.
- Gonzales, J.U., 2013. Gait performance in relation to aortic pulse wave velocity, carotid artery elasticity and peripheral perfusion in healthy older adults. *Clin. Physiol. Funct. Imaging* 33, 245–251.
- Gonzales, J.U., Wiberg, M., Defferari, E., Proctor, D.N., 2015. Arterial stiffness is higher in older adults with increased perceived fatigue and fatigability during walking. *Exp. Gerontol.* 61, 92–97.
- Greameux, V., Iskandar, M., Kervio, G., Deley, G., Perennou, D., Casillas, J.M., 2008. Comparative analysis of oxygen uptake in elderly subjects performing two walk tests: the six-minute walk test and the 200-m fast walk test. *Clin. Rehabil.* 22, 162–168.
- Hametner, B., Wassertheurer, S., 2017. Pulse waveform analysis: is it ready for prime time? *Curr. Hypertens. Rep.* 19, 73.
- Harrell, F.E., 2015. *Regression Modeling Strategies*, second ed. Springer International Publishing, Switzerland.
- Holland, A.E., Spruit, M.A., Troosters, T., Puhan, M.A., Pepin, V., Saey, D., McCormack, M.C., Carlin, B.W., Sciurba, F.C., Pitta, F., Wanger, J., MacIntyre, N., Kaminsky, D.A., Culver, B.H., Revill, S.M., Hernandez, N.A., Andrianopoulos, V., Camillo, C.A., Mitchell, K.E., Lee, A.L., Hill, C.J., Singh, S.J., 2014. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur. Respir. J.* 44, 1428–1446.
- Hwang, J.W., Kang, S.J., Lim, H.S., Choi, B.J., Choi, S.Y., Hwang, G.S., Yoon, M.H., Shin, J.H., Tahk, S.J., 2012. Impact of arterial stiffness on regional myocardial function assessed by speckle tracking echocardiography in patients with hypertension. *J. Cardiovasc. Ultrasound.* 20, 90–96.
- Infanger, D., Schmidt-Trucksäss, A., 2019. P value functions: an underused method to present research results and to promote quantitative reasoning. *Stat. Med.* 38, 4189–4197.
- Jakobsen, J.C., Gluud, C., Wetterslev, J., Winkel, P., 2017. When and how should multiple imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts. *BMC Med. Res. Methodol.* 17.
- Kasovic, M., Stefan, L., Stefan, A., 2021. Normative data for gait speed and height norm speed in >= 60-year-old men and women. *Clin. Interv. Aging* 16, 225–230.
- Kohn, J.C., Lampi, M.C., Reinhart-King, C.A., 2015. Age-related vascular stiffening: causes and consequences. *Front. Genet.* 6, 112.
- Kucharska-Newton, A.M., Stoner, L., Meyer, M.L., 2019. Determinants of vascular age: an epidemiological perspective. *Clin. Chem.* 65, 108–118.
- Lantelme, P., Laurent, S., Besnard, C., Bricca, G., Vincent, M., Legedz, L., Milon, H., 2008. Arterial stiffness is associated with left atrial size in hypertensive patients. *Arch. Cardiovasc. Dis.* 101, 35–40.
- Latham, R.D., Westerhof, N., Sipkema, P., Rubal, B.J., Reuderink, P., Murgo, J.P., 1985. Regional wave travel and reflections along the human aorta: a study with six simultaneous micromanometric pressures. *Circulation* 72, 1257–1269.
- Marzetti, E., Landi, F., Marini, F., Cesari, M., Buford, T.W., Manini, T.M., Onder, G., Pahor, M., Bernabei, R., Leeuwenburgh, C., Calvani, R., 2014. Patterns of circulating inflammatory biomarkers in older persons with varying levels of physical performance: a partial least squares-discriminant analysis approach. *Front. Med.* 1, 27.
- Mattace-Raso, F.U.S., Hofman, A., Verwoert, G.C., Witteman, J.C.M., Wilkinson, I., Cockcroft, J., McEniery, C., Yasmin, Laurent, S., Boutouyrie, P., Bozec, E., Hansen, T. W., Torp-Pedersen, C., Ibsen, H., Jeppesen, J., Vermeersch, S.J., Rietzschel, E., De Buyzere, M., Gillebert, T.C., Van Bortel, L., Segers, P., Vlachopoulos, C., Aznaouridis, C., Stefanadis, C., Benetos, A., Labat, C., Lacolley, P., Stehouwer, C.D. A., Nijpels, G., Dekker, J.M., Ferreira, I., Twisk, J.W.R., Czernichow, S., Galan, P., Herberg, S., Pannier, B., Guerin, A., London, G., Cruickshank, J.K., Anderson, S.G., Paini, A., Rosei, E.A., Muesan, M.L., Salvetti, M., Filipovsky, J., Seidlerova, J., Dolejsova, M., Stiffnes, R.V.A., 2010. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *Eur. Heart J.* 31, 2338–2350.
- Mitchell, G.F., 2008. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. *J. Appl. Physiol.* 105, 1652–1660.
- Nagai, Y., Metter, E.J., Fleg, J.L., 1999. Increased carotid artery intimal-medial thickness: risk factor for exercise-induced myocardial ischemia in asymptomatic older individuals. *Vasc. Med.* 4, 181–186.
- Nemcsik, J., Cseprekai, O., Tisler, A., 2017. Measurement of arterial stiffness: a novel tool of risk stratification in hypertension. *Adv. Exp. Med. Biol.* 956, 475–488.
- Netuveli, G., Wiggins, R.D., Hildon, Z., Montgomery, S.M., Blane, D., 2006. Quality of life at older ages: evidence from the English longitudinal study of aging (wave 1). *J. Epidemiol. Community Health* 60, 357–363.
- Nichols, W.W., McDonald, D.A., 1972. Wave-velocity in the proximal aorta. *Med. Biol. Eng.* 10, 327–335.
- Nunan, D., Wassertheurer, S., Lasserson, D., Hametner, B., Fleming, S., Ward, A., Heneghan, C., 2012. Assessment of central haemodynamics from a brachial cuff in a community setting. *BMC Cardiovasc. Disord.* 12, 48.
- Nürnberg, J., Michalski, R., Turk, T.R., Opazo Saez, A., Witzke, O., Kribben, A., 2011. Can arterial stiffness parameters be measured in the sitting position? *Hypertens. Res.* 34, 202–208.
- O'Rourke, M.F., Yaginuma, T., Avolio, A.P., 1984. Physiological and pathophysiological implications of ventricular/vascular coupling. *Ann. Biomed. Eng.* 12, 119–134.
- Ogawa, N., Nanayama Tanaka, C., Ishido, M., Nakamura, T., Nishiwaki, M., 2020. Poor walking speed is associated with higher segment-specific arterial stiffness in older adult Japanese community dwellers: a cross-sectional study. *Front. Physiol.* 11, 587215.
- Payne, G.W., Bearden, S.E., 2006. The microcirculation of skeletal muscle in aging. *Microcirculation* 13, 275–277.
- Perera, S., Mody, S.H., Woodman, R.C., Studenski, S.A., 2006. Meaningful change and responsiveness in common physical performance measures in older adults. *J. Am. Geriatr. Soc.* 54, 743–749.
- Pohrt, A., Kendel, F., Demuth, I., Drewelies, J., Nauman, T., Behloul, H., Stadler, G., Pilote, L., Regitz-Zagrosek, V., Gerstorff, D., 2022. Differentiating sex and gender among older men and women. *Psychosom. Med.* 84, 339–346.
- Portegijs, E., Karavirta, L., Saajanaho, M., Rantalainen, T., Rantanen, T., 2019. Assessing physical performance and physical activity in large population-based aging studies: home-based assessments or visits to the research center? *BMC Public Health* 19, 1570.
- Rantanen, T., Saajanaho, M., Karavirta, L., Siltanen, S., Rantakokko, M., Viljanen, A., Rantalainen, T., Pynnönen, K., Karvonen, A., Lisko, I., Palmberg, L., Eronen, J., Palonen, E.-M., Hinrichs, T., Kauppinen, M., Kokko, K., Portegijs, E., 2018. Active aging - resilience and external support as modifiers of the disablement outcome: AGNES study protocol. *BMC Public Health* 18, 565.
- Reshetnik, A., Gohlisch, C., Tolle, M., Zidek, W., Van Der Giet, M., 2017. Oscillometric assessment of arterial stiffness in everyday clinical practice. *Hypertens. Res.* 40, 140–145.
- Reuben, D.B., Seeman, T.E., Keeler, E., Hayes, R.P., Bowman, L., Sewall, A., Hirsch, S.H., Wallace, R.B., Guralnik, J.M., 2004. The effect of self-reported and performance-based functional impairment on future hospital costs of community-dwelling older persons. *Gerontologist* 44, 401–407.
- Sakari-Rantala, R., Era, P., Rantanen, T., Heikkinen, E., 1998. Associations of sensory-motor functions with poor mobility in 75- and 80-year-old people. *Scand. J. Rehabil. Med.* 30, 121–127.
- Sayers, S.P., Guralnik, J.M., Newman, A.B., Brach, J.S., Fielding, R.A., 2006. Concordance and discordance between two measures of lower extremity function: 400 meter self-paced walk and SPPB. *Aging Clin. Exp. Res.* 18, 100–106.
- Segers, P., Kips, J., Trachet, B., Swillens, A., Vermeersch, S., Mahieu, D., Rietzschel, E., De Buyzere, M., Van Bortel, L., 2009. Limitations and pitfalls of non-invasive measurement of arterial pressure wave reflections and pulse wave velocity. *Artery Res.* 3, 79–88.
- Simonsick, E.M., Schrack, J.A., Glynn, N.W., Ferrucci, L., 2014. Assessing fatigability in mobility-intact older adults. *J. Am. Geriatr. Soc.* 62, 347–351.
- Studenski, S., Perera, S., Patel, K., Rosano, C., Faulkner, K., Inzitari, M., Brach, J., Chandler, J., Cawthon, P., Connor, E.B., Nevitt, M., Visser, M., Kritchevsky, S., Badinelli, S., Harris, T., Newman, A.B., CAuley, J., Ferrucci, L., Guralnik, J., 2011. Gait speed and survival in older adults. *JAMA* 305, 50–58.
- Sugawara, J., Hayashi, K., Yokoi, T., Tanaka, H., 2010. Carotid-femoral pulse wave velocity: impact of different arterial path length measurements. *Artery Res.* 4, 27–31.

- Sutton-Tyrrell, K., Najjar, S.S., Boudreau, R.M., Venkitachalam, L., Kupelian, V., Simonsick, E.M., Havlik, R., Lakatta, E.G., Spurgeon, H., Kritchevsky, S., Pahor, M., Bauer, D., Newman, A., Health, A.B.C.S., 2005. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. *Circulation* 111, 3384–3390.
- Townsend, R.R., Wilkinson, I.B., Schiffrin, E.L., Avolio, A.P., Chirinos, J.A., Cockcroft, J. R., Heffernan, K.S., Lakatta, E.G., McEniery, C.M., Mitchell, G.F., Najjar, S.S., Nichols, W.W., Urbina, E.M., Weber, T., <collab>American Heart Association Council on, H.collab, 2015. Recommendations for improving and standardizing vascular research on arterial stiffness: a scientific statement from the American Heart Association. *Hypertension* 66, 698–722.
- van Kan, G.A., Rolland, Y., Andrieu, S., Bauer, J., Beauchet, O., Bonnefoy, M., Cesari, M., Donini, L.M., Gillette-Guyonnet, S., Inzitari, M., Nourhashemi, F., Onder, G., Ritz, P., Salva, A., Visser, M., Vellas, B., 2009. Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people - an International Academy on Nutrition and Aging (Iana) Task Force. *J.Nutr.HealthAging* 13, 881–889.
- van Buuren, S., 2018. Flexible imputation of missing data, 2nd ed. Chapman and Hall/CRC, New York.
- Vink, D., Aartsen, M.J., Schoevers, R.A., 2008. Risk factors for anxiety and depression in the elderly: a review. *J. Affect. Disord.* 106, 29–44.
- Virmani, R., Avolio, A.P., Mergner, W.J., Robinowitz, M., Herderick, E.E., Cornhill, J.F., Guo, S.Y., Liu, T.H., Ou, D.Y., O'Rourke, M., 1991. Effect of aging on aortic morphology in populations with high and low prevalence of hypertension and atherosclerosis. Comparison between occidental and Chinese communities. *Am. J. Pathol.* 139, 1119–1129.
- Vlachopoulos, C., Aznaouridis, K., Stefanadis, C., 2010. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J. Am. Coll. Cardiol.* 55, 1318–1327.
- Vlachopoulos, C., Xaplanteris, P., Aboyans, V., Brodmann, M., Cifkova, R., Cosentino, F., De Carlo, M., Gallino, A., Landmesser, U., Laurent, S., Lekakis, J., Mikhailidis, D.P., Naka, K.K., Protogerou, A.D., Rizzoni, D., Schmidt-Trucksass, A., Van Bortel, L., Weber, T., Yamashina, A., Zimlichman, R., Boutouyrie, P., Cockcroft, J., O'Rourke, M., Park, J.B., Schillaci, G., Sillesen, H., Townsend, R.R., 2015. The role of vascular biomarkers for primary and secondary prevention. A position paper from the European Society of Cardiology Working Group on peripheral circulation: endorsed by the Association for Research into Arterial Structure and Physiology (ARTERY) Society. *Atherosclerosis* 241, 507–532.
- von Bonsdorff, M., Rantanen, T., Laukkanen, P., Suutama, T., Heikkinen, E., 2006. Mobility limitations and cognitive deficits as predictors of institutionalization among community-dwelling older people. *Gerontology* 52, 359–365.
- Wassertheurer, S., Kropf, J., Weber, T., van der Giet, M., Baulmann, J., Ammer, M., Hametner, B., Mayer, C.C., Eber, B., Magometschnigg, D., 2010. A new oscillometric method for pulse wave analysis: comparison with a common tonometric method. *J. Hum. Hypertens.* 24, 498–504.
- Wassertheurer, S., Mayer, C., Breitenecker, F., 2008. Modeling arterial and left ventricular coupling for non-invasive measurements. *Simul. Model. Pract. Theory* 16, 988–997.
- Watson, N.L., Sutton-Tyrrell, K., Youk, A.O., Boudreau, R.M., Mackey, R.H., Simonsick, E.M., Rosano, C., Hardy, S.E., Windham, B.G., Harris, T.B., Najjar, S.S., Lakatta, E.G., Atkinson, H.H., Johnson, K.C., Bauer, D.C., Newman, A.B., Health, A. B.C.S., 2011. Arterial stiffness and gait speed in older adults with and without peripheral arterial disease. *Am. J. Hypertens.* 24, 90–95.
- Weber, T., Wassertheurer, S., Rammer, M., Maurer, E., Hametner, B., Mayer, C.C., Kropf, J., Eber, B., 2011. Validation of a brachial cuff-based method for estimating central systolic blood pressure. *Hypertension* 58, 825–832.
- Yoon, S.K., Kim, H.N., Song, S.W., 2020. Associations of skeletal muscle mass with atherosclerosis and inflammatory markers in Korean adults. *Arch. Gerontol. Geriatr.* 90, 104163.
- Zieman, S.J., Melenovsky, V., Kass, D.A., 2005. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler. Thromb. Vasc. Biol.* 25, 932–943.