



LJMU Research Online

van der Sluijs, K, Bakker, E, Kerstens, T, Stens, N, de Koning, I, Thannhauser, J, Malik, A, Reesink, K, Nabeel, PM, Raj, K, Joseph, J, Allard, NAE, Berge, K, Bongers, CCWG, Brouwer, CG, Hartman, YAW, Hazeleger, LR, Hopman, MTE, Janssen, SLJE, Janssen Daalen, JM, Kersten, BTP, Koopmans, L, Kroesen, SH, Landman, TRJ, Luiken, TTJ, Mast, IH, Peggen, MAG, Schoofs, MCA, Schreurs, BA, Vermeulen, JJM, Vloet, JIA, Wanders, L, Eijsvogels, T and Thijssen, D

Association of Objectively Measured Sedentary Behavior With Arterial Stiffness: Findings From the Nijmegen Exercise Study

<http://researchonline.ljmu.ac.uk/id/eprint/24947/>

Article

Citation (please note it is advisable to refer to the publisher's version if you intend to cite from this work)

van der Sluijs, K, Bakker, E, Kerstens, T, Stens, N, de Koning, I, Thannhauser, J, Malik, A, Reesink, K, Nabeel, PM, Raj, K, Joseph, J, Allard, NAE, Berge, K, Bongers, CCWG, Brouwer, CG, Hartman, YAW, Hazeleger, LR, Hopman, MTE, Janssen, SLJE, Janssen Daalen, JM, Kersten, BTP.

LJMU has developed [LJMU Research Online](http://researchonline.ljmu.ac.uk/) for users to access the research output of the University more effectively. Copyright © and Moral Rights for the papers on this site are retained by the individual authors and/or other copyright owners. Users may download and/or print one copy of any article(s) in LJMU Research Online to facilitate their private study or for non-commercial research. You may not engage in further distribution of the material or use it for any profit-making activities or any commercial gain.

The version presented here may differ from the published version or from the version of the record. Please see the repository URL above for details on accessing the published version and note that access may require a subscription.



<http://researchonline.ljmu.ac.uk/>

For more information please contact researchonline@ljmu.ac.uk

<http://researchonline.ljmu.ac.uk/>

ORIGINAL ARTICLE OPEN ACCESS

Association of Objectively Measured Sedentary Behavior With Arterial Stiffness: Findings From the Nijmegen Exercise Study

Koen M. van der Sluijs¹  | Esmée A. Bakker^{1,2} | Thijs P. Kerstens¹ | Niels A. Stens^{1,3}  | Iris A. de Koning¹ | Jos Thannhauser^{1,3} | Afrah E. F. Malik⁴ | Koen D. Reesink⁴ | P. M. Nabeel⁵ | Kiran V. Raj⁵ | Jayaraj Joseph⁶ | Nijmegen Exercise Study collaboration¹ | Thijs M. H. Eijsvogels¹ | Dick H. J. Thijssen¹

¹Department of Medical BioSciences, Radboud University Medical Center, Nijmegen, The Netherlands | ²Department of Physical Education and Sports, Faculty of Sports Science, Sport and Health University Research Institute (iMUDS), University of Granada, Granada, Spain | ³Department of Cardiology, Radboud University Medical Center, Nijmegen, The Netherlands | ⁴Department of Biomedical Engineering, Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, The Netherlands | ⁵Healthcare Technology Innovation Centre, Indian Institute of Technology Madras, Chennai, India | ⁶Department of Electrical Engineering, Indian Institute of Technology Madras, Chennai, India

Correspondence: Koen M. van der Sluijs (koen.vandersluijs@radboudumc.nl)

Received: 23 May 2024 | **Revised:** 7 October 2024 | **Accepted:** 24 October 2024

Funding: This work was supported by Horizon 2020 Framework Programme and ZonMw.

Keywords: arterial stiffness | cardiovascular disease | pulse wave velocity | sedentary behavior | thigh-worn accelerometry

ABSTRACT

Sedentary behavior (SB) may affect arterial stiffness, preceding the development of cardiovascular disease. We investigated the association of objectively measured SB with arterial stiffness. We also investigated factors that affected this association. We recruited adult volunteers and measured SB with thigh-worn accelerometry for 24 hrs/day for eight consecutive days. Central (carotid-femoral pulse wave velocity, cfPWV, gold standard) and local carotid arterial stiffness (stiffness index Beta and pressure-strain elasticity E_p) were measured with ultrasound. Linear regression was used and adjusted for demographics, cardiometabolic factors, and moderate-to-vigorous physical activity (MVPA) volume. Effect modification was studied with interaction terms. Participants ($N=664$, 64 (standard deviation: 11, range: 23–89) years, 397 (59.8%) male) demonstrated 9.1 (1.6) hrs/day of SB, and arterial stiffness was 8.6 (3.0) m/s for cfPWV, 6.4 (2.9) for Beta, and 87 (43) kPa for E_p . SB was not associated with cfPWV ($\beta=0.04$ 95% CI (–0.11, 0.18), $p=0.60$). The association of SB with local arterial stiffness was modified by systolic blood pressure (SBP) and MVPA volume. Stratified analyses revealed positive associations of SB with Beta ($\beta=0.29$ (0.05, 0.53), $p=0.016$) and E_p ($\beta=4.83$ (1.39, 8.27), $p=0.006$) in participants with SBP > 134 mmHg or > 103 min/day of MVPA ($\beta=0.23$ (0.03, 0.42), $p=0.024$ and $\beta=3.55$ (0.82, 6.29), $p=0.011$, respectively). We found no association of objectively measured SB with central arterial stiffness. However, SB was positively associated with local carotid stiffness in participants with higher SBP or MVPA levels. In certain subgroups, SB may affect carotid arterial stiffening, reinforcing the relation between SB and cardiovascular disease.

1 | Introduction

The detrimental effects of sedentary behavior (SB) on health are well-documented [1, 2]. High volumes of SB are associated with an increased risk of cardiovascular disease (CVD) and

all-cause and CVD-related mortality [3, 4]. Accordingly, the World Health Organization's guidelines on physical activity and sedentary behavior recommend limiting the time spent sedentary and replacing SB with physical activity of any intensity [5]. To better tailor prevention programs, a deeper

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2024 The Author(s). *Scandinavian Journal of Medicine & Science in Sports* published by John Wiley & Sons Ltd.

understanding of the effects of SB on the development of CVD is required.

Previous studies have demonstrated that high arterial stiffness is related to the development of CVD [6–8]. A recent meta-analysis highlighted that arterial stiffening precedes hypertension [9] and may therefore contribute to the development of CVD. Exposure to excessive levels of SB may affect arterial stiffness, which may in part explain the relation between SB and CVD. Studies found that SB acutely reduces shear stress and nitric oxide availability, which subsequently increases inflammation and oxidative stress [10, 11]. These factors promote endothelial dysfunction and may thereby contribute to arterial stiffening [6, 12]. Nonetheless, the association of SB with arterial stiffness remains unclear, primarily since previous studies [11, 13] did not adopt current gold standard procedures to objectively evaluate SB (i.e., thigh-worn accelerometry [14, 15]).

Therefore, we investigated the associations of objectively measured SB with measures of central and local arterial stiffness. We hypothesized that a positive association exists between SB and arterial stiffness. In addition, we aimed to explore potential effect modification across subgroups.

2 | Materials and Methods

2.1 | Study Design and Population

Adult volunteers were recruited from the Nijmegen Exercise Study, a prospective cohort study of Dutch individuals aiming to better understand the impact of lifestyle on disease development [16]. Recruitment for the present sub-study took place between May 2021 and March 2023. Inclusion criteria were Dutch residency and language proficiency, and pregnant women were excluded from the present study. Participants were physically examined during a single visit to our research center at the Radboud University Medical Center (Nijmegen, the Netherlands). All participants provided written informed consent. The local Medical Research Ethics Committee of the region Arnhem-Nijmegen provided approval (NL36743.091.11), and the study was conducted in accordance with the Declaration of Helsinki.

2.2 | Data Collection

2.2.1 | Demographics

Demographics were collected via online questionnaires and included: age, sex, level of education, employment status, alcohol consumption [glasses/wk], smoking behavior [current smoker, former smoker, never smoked], performance of resistance exercise, medical history, and medication use. Level of education was specified as low (i.e., primary school or basic vocational education), intermediate (i.e., secondary school or secondary vocational education), or high (i.e., higher vocational education or academic education). Participants were categorized into the “control,” “cardiovascular risk factors (CVRF),” or “CVD” group based on medical history and medication use. Participants were assigned to the CVRF group if 1) they reported having

hypertension, hypercholesterolemia, or diabetes mellitus and used antihypertensive, cholesterol-lowering, or diabetic medication, or if 2) they presented with total cholesterol, fasted glucose, or non-fasted glucose concentration greater than 6.5, 6.9, or 11.0 mmol/L, respectively, at the research visit. Participants who reported a history of myocardial infarction, heart failure, stroke, or thrombosis and who used cardiovascular medication were assigned to the CVD group. Individuals were assigned to the control group in case of the absence of CVRF and CVD [17, 18].

2.2.2 | Physical Examination

We assessed the health characteristics of our participants during their visit to our research center. Participants were instructed to fast for at least 4 h, refrain from strenuous exercise for 24 h, and refrain from alcohol and caffeine for 18 h prior to their visit. We measured height [cm] and body mass [kg] (Seca GmbH & Co. KG, Hamburg, Germany), and we computed body mass index [kg/m^2]. Non-invasive left brachial systolic blood pressure (SBP, [mmHg]), diastolic blood pressure (DBP, [mmHg]), and resting heart rate [beats/min] were measured twice (M3; OMRON, Kyoto, Japan) after at least five minutes of rest in supine position; average values were used for analysis. Venous blood was sampled (SST II Advance, 8.5 mL; BD Vacutainer, Franklin Lakes, NJ, USA) and coagulated for 45 to 60 min before being centrifuged at 3000 revolutions/min for 10 min at 4°C. Serum was then transferred to 2 mL microtubes and stored at –80°C until analysis. The concentration of the following biomarkers was determined: total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, glucose hexokinase (all in [mmol/L]), insulin [$\mu\text{IU}/\text{mL}$], creatinine [$\mu\text{mol}/\text{L}$], high-sensitive cardiac troponin I (hs-cTnI, [ng/L]), N-terminal pro-B-type-natriuretic-peptide (NT-proBNP, [pmol/L]), and C-reactive protein [mg/L]. Analyses were performed batchwise on Atellica (and IMMULITE 2000 for insulin) analyzers (Siemens Healthcare, Erlangen, Germany) in the Gelderse Vallei Hospital, Ede, the Netherlands.

2.2.3 | Sedentary Behavior and Physical Activity

SB was assessed over a period of eight consecutive days using the activPAL3 micro triaxial accelerometer (PAL Technologies Ltd., Glasgow, UK). During this period, participants were instructed to wear the accelerometer on their right thigh for 24 hrs/day and requested to keep a sleep/wake diary to enable automated analysis. Data were extracted via PALbatch (PAL Software Suite version 8, PAL Technologies Ltd.) and analyzed using a modified version of the script by Winkler et al. [19, 20] in SAS (Statistical Analysis System, RRID:SCR_008567, version 9.4; SAS Institute Inc., Cary, NC, USA). SB was primarily expressed as total sitting time [hrs/day]. To investigate the relation between spending time in prolonged sedentary bouts (≥ 30 min) on arterial stiffness, we used the relative bout-to-total sitting time (RelBST, [%]), expressed as the percentage of cumulative time spent in prolonged sedentary bouts relative to the total sitting time. Other accelerometry parameters included time spent in light physical activity (LIPA) and moderate-to-vigorous physical activity (MVPA) [min/day], sleeping time [hrs/day], and step count [steps/day].

2.2.4 | Arterial Stiffness

Arterial stiffness was assessed with non-invasive, image-free ultrasound technology using the ARTSENS Plus (Healthcare Technology Innovation Centre, Indian Institute of Technology Madras, Chennai, India) [21]. Measurements were performed in supine position after ten minutes of rest, following the expert consensus document on the measurement of aortic stiffness [22]. Left brachial blood pressure and heart rate were obtained by the integrated blood pressure monitor and used for the acquisition of local arterial stiffness parameters. The distension of the left common carotid artery was tracked with amplitude-mode (A-mode) ultrasound at a sampling frequency of 250 Hz, from which the dimensionless stiffness index Beta [a.u.] and the pressure-strain elasticity E_p [kPa] were computed, two measures of local arterial stiffness [21, 23, 24]. Central arterial stiffness was quantified using the carotid-femoral pulse wave velocity (cfPWV, [m/s]), the gold standard for arterial stiffness assessment [25]. For this purpose, a thigh cuff was inflated to monitor the femoral artery pressure waveforms. The carotid-femoral pulse transit time was determined from the A-mode carotid ultrasound recording and the cuff-based femoral artery pressure waveforms using the intersecting tangent algorithm [26]. The path length was estimated by subtracting the distance from the carotid artery site to the sternal notch and the distance from the femoral artery site to the thigh cuff from the distance between the sternal notch and the thigh cuff [27]. Finally, cfPWV was calculated by dividing the path length by the pulse transit time.

2.3 | Statistical Analysis

Statistical analyses were performed in R (version 4.3.2, RRID:SCR_001905), and p -values < 0.05 were considered statistically significant. Results were presented as mean (standard deviation), median [first quartile, third quartile], or number (percentage), as appropriate. Participant characteristics were stratified for sex and were tested using independent samples t -test, Mann-Whitney U test, or chi-squared test, as appropriate.

We performed linear regression analyses to investigate the association of SB with arterial stiffness and included only individuals with complete exposure, outcome, and covariate data. We created univariable regression models for cfPWV, Beta, and E_p with total sitting time as the dependent variable. Next, we adjusted these models for a priori selected confounders, that is, age, sex, employment status, smoking behavior, cardiovascular health group, body mass index, SBP (as acquired by the ARTSENS Plus), total cholesterol and C-reactive protein concentrations, and time spent in MVPA. Subsequently, we extended these models by one interaction term at a time to investigate potential effect modification across subgroups. In case of significant effect modification, we calculated the unstandardized regression coefficient (β) and 95% confidence interval in each stratum of the categorical variable or in subgroups based on a median split of the continuous variable. Non-linear relations were explored by regressing cfPWV on the square of total sitting time, but no evidence for such a relationship was found (data not presented). Finally, similar regression analyses were performed to investigate the associations of RelBST with the three arterial

stiffness measures. These analyses followed the same procedure but used RelBST as the dependent variable and were additionally adjusted for total sitting time.

3 | Results

A total of 1417 participants visited our research center to undergo physical examination between May 2021 and May 2023. Arterial stiffness was measured in a subset of $N = 758$ participants. Analyses of the present study were performed on individuals with complete exposure, outcome, and covariate data, resulting in an analytic sample of $N = 664$ individuals. These participants had a mean age of 64 (standard deviation: 11, range: 23–89) years and were most frequently male (i.e., 397 (60%) male and 267 (40%) female, Table 1). On average, participants spent 9.1 (1.6) hrs/day sitting and accumulated 50 (12) % of their total sitting time in prolonged (i.e., > 30 min) sedentary bouts. Participants had a mean cfPWV of 8.6 (3.0) m/s, and local arterial stiffness measures Beta and E_p were on average 6.4 (2.9) a.u. and 87 (43) kPa, respectively.

3.1 | Association of Sedentary Behavior With Arterial Stiffness

Univariable linear regression analyses showed no associations of SB parameters and central or local arterial stiffness measures (Figure 1, Figure S1, <https://doi.org/10.6084/m9.figshare.25664388>). After adjustment for confounders, total sitting time and cfPWV were not associated ($\beta = 0.04$ ($-0.11, 0.18$), $p = 0.60$), but local arterial stiffness measures Beta and E_p were positively associated with total sitting time (Figure 2). Multivariable analyses revealed no associations of RelBST with central or local stiffness measures ($\beta = 0.003$ ($-0.01, 0.02$), $p = 0.71$ for cfPWV; $\beta = 0.006$ ($-0.01, 0.02$), $p = 0.53$ for Beta; $\beta = 0.07$ ($-0.19, 0.32$), $p = 0.60$ for E_p).

3.2 | Factors Modifying the Association of Sedentary Behavior With Arterial Stiffness

No evidence was found supporting effect modification across subgroups for the association of total sitting time with cfPWV. In contrast, total sitting time was positively associated with measures of local arterial stiffness in participants with values above the median for SBP (> 134 mmHg) and time spent in MVPA (> 103 min/day, Figure 2, Tables S1–S2, <https://doi.org/10.6084/m9.figshare.25664448>). We performed additional, explorative regression analyses in three subgroups based on tertiles of SBP and MVPA volume. We found similar results, indicating significant positive associations of total sitting time with both measures of local arterial stiffness in the highest tertiles of SBP and MVPA volume (data not shown). Furthermore, the effect of RelBST on cfPWV in participants who never smoked seemed to be the opposite of the effect in former smokers. Stratified analyses revealed no significant associations in either of these subgroups ($\beta = 0.02$ ($-0.006, 0.05$), $p = 0.13$ for participants who never smoked; $\beta = -0.02$ ($-0.05, 0.007$), $p = 0.15$ for former smokers). No effect modification was observed for the associations of RelBST with Beta and E_p .

TABLE 1 | Participant characteristics of the total sample and stratified by sex.

	Total sample N = 664	Female N = 267	Male N = 397	p
<i>Demographics</i>				
Age, yrs	64 (11)	62 (12)	66 (10)	<0.001
Male sex	397 (59.8)	0 (0)	397 (100)	<0.001
Level of education				<0.001
Low	49 (7.4)	11 (4.1)	38 (9.6)	
Intermediate	260 (39.2)	133 (49.8)	127 (32.0)	
High	355 (53.5)	123 (46.1)	232 (58.4)	
Employed	342 (51.5)	152 (56.7)	191 (48.0)	0.027
Alcohol consumption, glasses/wk ^a	4 [1, 8]	3 [1, 6]	5 [2, 10]	<0.001
Smoking behavior				0.42
Current smoker	37 (5.6)	11 (4.1)	26 (6.5)	
Former smoker	287 (43.2)	118 (44.2)	169 (42.6)	
Never smoked	340 (51.2)	138 (51.7)	202 (50.9)	
Performing resistance exercise ^b	201 (30.5)	87 (32.8)	114 (28.9)	0.30
<i>Comorbidities</i>				
Hypertension ^c	161 (24.5)	60 (22.6)	101 (25.8)	0.41
Hypercholesterolemia ^d	132 (20.3)	39 (14.9)	93 (24.0)	0.005
Diabetes ^e	24 (3.7)	6 (2.3)	18 (4.6)	0.14
Myocardial infarction ^f	33 (5.0)	3 (1.1)	30 (7.6)	<0.001
Heart failure ^b	23 (3.5)	4 (1.5)	19 (4.8)	0.029
Stroke ^f	30 (4.5)	10 (3.7)	20 (5.1)	0.45
Thrombosis ^e	17 (2.6)	8 (3.1)	9 (2.3)	0.62
Cardiovascular health group				<0.001
Control	400 (60.2)	175 (65.5)	225 (56.7)	
Cardiovascular risk factors	195 (29.4)	79 (29.6)	116 (29.2)	
Cardiovascular disease	69 (10.4)	13 (4.9)	56 (14.1)	
<i>Physical examination</i>				
Body mass index, kg/m ²	24.4 (3.1)	23.6 (3.6)	25.0 (2.6)	<0.001
Systolic blood pressure, mmHg	139 (17)	136 (19)	141 (16)	<0.001
Diastolic blood pressure, mmHg	83 (9)	82 (9)	84 (9)	0.001
Resting heart rate, beats/min	60 (10)	61 (9)	59 (10)	<0.001
Total cholesterol, mmol/L	5.2 [4.6, 6.0]	5.6 [4.9, 6.3]	5.0 [4.3, 5.8]	<0.001
HDL cholesterol, mmol/L	1.6 [1.3, 1.9]	1.8 [1.6, 2.1]	1.4 [1.2, 1.7]	<0.001
LDL cholesterol, mmol/L	2.9 [2.3, 3.5]	3.0 [2.4, 3.6]	2.9 [2.2, 3.5]	0.22
Triglycerides, mmol/L	1.0 [0.8, 1.3]	1.0 [0.7, 1.3]	1.0 [0.8, 1.4]	0.017
Glucose, mmol/L ^g	5.0 [4.7, 5.3]	5.0 [4.7, 5.2]	5.0 [4.7, 5.4]	0.013
Insulin, μ IU/mL	2.9 [2.0, 5.8]	2.5 [2.0, 5.0]	3.3 [2.0, 6.3]	0.009
Creatinine, μ mol/L	77 [67, 85]	67 [61, 73]	83 [75, 91]	<0.001

(Continues)

TABLE 1 | (Continued)

	Total sample N=664	Female N=267	Male N=397	p
C-reactive protein, mg/L	4.0 [4.0, 4.0]	4.0 [4.0, 4.0]	4.0 [4.0, 4.0]	0.44
Hs-cTnI, ng/L ^h	4.5 [2.7, 7.9]	3.1 [2.5, 5.6]	5.5 [3.5, 9.1]	<0.001
NT-proBNP, pmol/L ⁱ	11.0 [6.0, 19.0]	12.0 [7.0, 19.0]	10.0 [5.0, 19.0]	0.093
Time spent in LIPA, min/day	282 (80)	299 (75)	270 (82)	<0.001
Time spent in MVPA, min/day	108 (38)	110 (38)	106 (38)	0.13
Sleeping time, hrs/day	8.4 (1.3)	8.6 (1.3)	8.3 (1.2)	0.001
Step count, steps/day	13 833 (4795)	14 302 (4713)	13 518 (4830)	0.039

Note: Results were presented as mean (standard deviation), median [first quartile, third quartile], or number (percentage), as appropriate. Variables marked with symbols describe ^aN=655, ^bN=660, ^cN=657, ^dN=650, ^eN=656, ^fN=661, ^gN=631, ^hN=659, ⁱN=663 participants.

Abbreviations: HDL, high-density lipoprotein; hs-cTnI, high-sensitive cardiac troponin I; LDL, low-density lipoprotein; LIPA, light physical activity; MVPA, moderate-to-vigorous physical activity; NT-proBNP, N-terminal pro-B-type-natriuretic peptide.

4 | Discussion

To our knowledge, our study is the first to evaluate the associations of objectively measured SB using thigh-worn accelerometry with measures of central and local arterial stiffness while we also explored effect modification across subgroups. In participants of the Nijmegen Exercise Study, we found no association of SB with central arterial stiffness (i.e., cfPWV) and did not identify variables modifying this association. In contrast, positive associations of SB with local arterial stiffness measures (i.e., stiffness index Beta and pressure-strain elasticity E_p) were found, especially in individuals with higher levels of SBP or time spent in MVPA. These findings suggest that SB may affect local rather than central arterial stiffness and that the strength of this relationship may differ across subgroups.

In contrast to our hypothesis, we found no association of SB with cfPWV, the gold standard for measuring arterial stiffness [25]. Moreover, we observed no effect modification regarding this association. Previous studies in this area have presented conflicting results [13]. Similar to our findings, most studies on the long-term effects of SB reported no association of SB with cfPWV after adjustment for confounders [28–31]. Studies reporting a positive association of SB with cfPWV did not adjust for physical activity level in their models [32, 33] or found an association in the most sedentary quartile only [34]. Importantly, previous studies examining the potential relation between SB and arterial stiffness did not use thigh-worn devices, which is highly relevant as these devices are currently considered the gold standard for the assessment of SB. A key advantage of thigh-worn devices is their ability to distinguish sitting from standing postures, crucial in evaluating SB [14, 15]. The use of thigh-worn accelerometry therefore substantiates the validity and novelty of the present study. Given the widespread recognition and adoption of cfPWV as the gold standard for arterial stiffness assessment [25], the current lack of association between cfPWV and SB is highly relevant. The overall evidence from this and previous studies suggests that SB may not be directly associated with central arterial stiffness. This warrants further research on investigating via which mechanisms SB may be harmful to cardiovascular health.

Unlike our observations for central arterial stiffness, we found a significant positive association of SB with local carotid arterial stiffness after adjustment for confounders. This finding reinforces the observations of previous studies on this topic [35, 36]. Importantly, prior studies employed various measures to quantify local carotid stiffness [23, 24, 35, 36], illustrating the novelty and lack of consensus within this research field. Interestingly, we found that the association of SB with carotid arterial stiffness was modified by two factors: SBP and time spent in MVPA. Regarding SBP, we observed that the individuals with higher SBP (i.e., >134 mmHg) are less healthy than those with a lower SBP (i.e., <134 mmHg) in terms of cardiometabolic markers (e.g., higher prevalence of CVRF, body mass index, glucose concentration, and carotid stiffness measures). The poorer cardiometabolic health may reflect some degree of endothelial dysfunction, making the carotid arteries more susceptible to stiffening in response to SB [10, 11]. These findings suggest that excessive sitting may have the largest impact on those who already are at increased risk of CVD, which emphasizes the importance of limiting SB. Further research is warranted to investigate this hypothesis.

In addition, SB was more strongly related to local arterial stiffness in those spending more time in MVPA. This contradicts the assumption that sedentariness is most strongly associated with cardiovascular outcomes in those who are inactive [1, 3]. Importantly, despite the significant interaction term, the effect estimates were positive in both the lower and higher MVPA volume subgroups, and the difference between estimates was small. The effect modification by time spent in MVPA in our data may thus be limited. The modification by time spent in MVPA is most likely explained by the overall activity levels of our sample since all 664 participants meet the minimum physical activity level as proposed by the World Health Organization guidelines [5]. The relatively high level of MVPA in our sample may potentially offset the association of SB with carotid arterial stiffness. Alternatively, the stronger association in those with higher MVPA volumes may relate to differences in total sitting time between the two subgroups. Another explanation could be that the subgroup with higher levels of MVPA represents fitter individuals who also perform more resistance exercise, which may be related to increased arterial stiffness [37]. However, our questionnaire data revealed no such difference between the

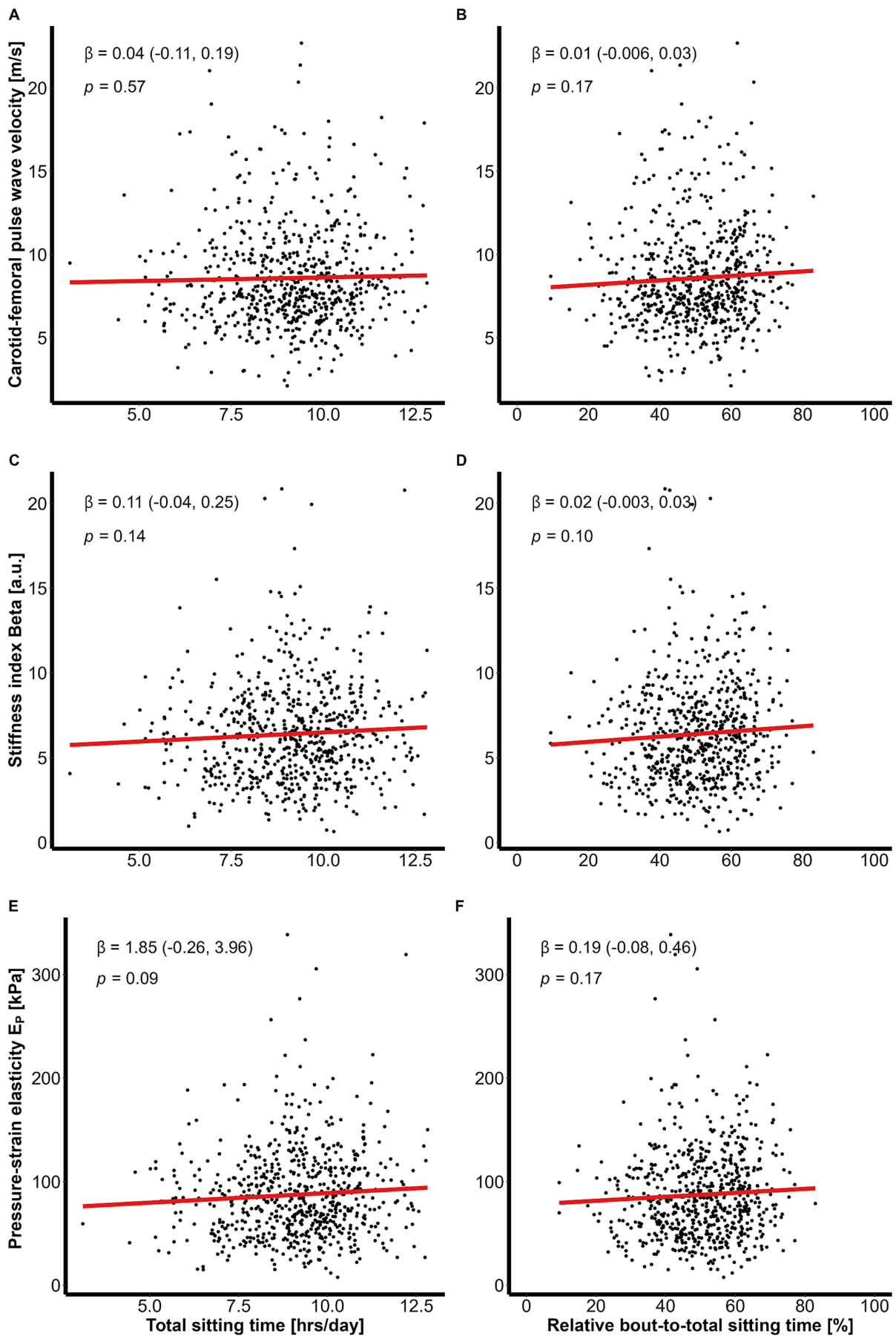


FIGURE 1 | Legend on next page.

FIGURE 1 | Univariable associations of sedentary behavior with arterial stiffness measures. Associations of total sitting time (left panels) and relative bout-to-total sitting time (right panels), with (A–B) carotid-femoral pulse wave velocity, (C–D) stiffness index Beta, and (E–F) pressure-strain elasticity E_p . Each dot represents an individual data point, and the red line represents the linear regression model. β indicates the regression coefficient and 95% confidence interval.

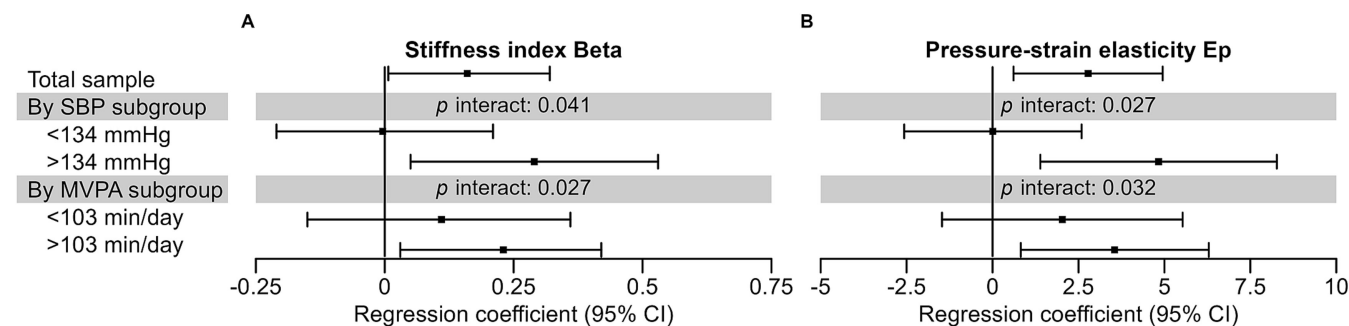


FIGURE 2 | Multivariable associations of total sitting time with local arterial stiffness measures. Regression coefficients describing the association of total sitting time with (A) stiffness index Beta and (B) pressure-strain elasticity E_p when adjusted for age, sex, employment status, smoking behavior, cardiovascular health group, body mass index, SBP, total cholesterol and C-reactive protein concentrations, and time spent in MVPA. Results are presented for the total sample and for subgroups based on a median split of effect-modifying variables (i.e., SBP and time spent in MVPA). CI, Confidence interval; MVPA, Moderate-to-vigorous physical activity; SBP, Systolic blood pressure.

subgroups. Finally, residual confounding (e.g., by menopausal status) could have distorted the current findings although we expect that our models were adjusted adequately for relevant confounders. Taken together, SB was associated to local carotid arterial stiffness, reinforcing the findings of previous studies. Nonetheless, the limited amount of evidence in this research field and the counterintuitive effect modification by MVPA volume warrant additional research to provide context to the current findings. Moreover, further research is needed to investigate if the current findings are generalizable, to investigate causality, and to identify subgroups that may be more prone to carotid arterial stiffening as a result of sedentariness.

An unexpected observation is that SB is associated with local but not central arterial stiffness. Aortic and carotid arterial beds are closely related in terms of biomechanical properties, characterized by elastic fibers with little musculature [38]. In addition, both aortic and carotid stiffness are known to increase with age and in the presence of CVRF [39]. Although a correlation between aortic and carotid stiffness parameters is observed, this correlation is not strong [40], and both aortic and carotid arterial stiffness are independently associated with increased risk of cardiovascular events [7, 8, 41, 42]. This suggests that aortic and carotid stiffness are related but are not the same, which may explain the discrepancy between the associations of SB with local and central arterial stiffness. A difference between these arteries that may explain the different associations with sedentary behavior relates to blood flow. Whilst various regulatory mechanisms attenuate substantial blood flow fluctuations and attempt to keep carotid blood flow stable [43], aortic blood flow can vary markedly. Nonetheless, exposure to prolonged periods of sedentary time causes reductions in cerebral perfusion [44] and therefore also lowers blood flow through the carotid arteries. Although these decreases in perfusion can be counteracted by physical activity, moderate-to-high-intensity exercise only minimally elevates cerebral blood flow velocity by 10%–20% [43, 45]. In

marked contrast, large flow fluctuations are present in the aorta during physical activities, with little work that examined the impact of sedentary time on aortic blood flow responses. The relatively large effects of SB on local carotid artery blood flow, compared to aortic blood flow, may contribute to these differences between arteries in relation to SB.

4.1 | Strengths and Limitations

The current study has several strengths. Thigh-worn accelerometry was used, which is superior to questionnaires but also to wrist- or hip-worn accelerometry for assessing SB [14, 15]. Furthermore, due to our sample size and comprehensive evaluations, we were able to adjust for multiple relevant confounders in our analyses of both central and local arterial stiffness. The study also has some limitations. As an individual's SB varies over the course of his/her life and arterial stiffness takes prolonged periods of time to adjust, longitudinal and repeated analyses seem most suitable for assessing the impact of SB on arterial stiffness. Another limitation of the current cross-sectional analysis is that causation cannot be inferred. Nonetheless, our findings provide novel insights into the association of SB with central and local arterial stiffness.

4.2 | Conclusion

SB assessed with thigh-worn accelerometry was not associated with central arterial stiffness among 664 individuals of the Nijmegen Exercise Study cohort, and this association was consistent across subgroups. Conversely, SB was associated with local arterial stiffness. Notably, those with higher levels of SBP or time spent in MVPA showed stronger associations of SB with local arterial stiffness than those with lower levels. These findings suggest that SB is associated with stiffness of the carotid arteries in certain subgroups, even after adjustment for relevant confounders influencing arterial stiffening. Given the known

risks of increased carotid arterial stiffness, larger volumes of SB may contribute to the development of CVD. Further research is required to longitudinally evaluate the effect of sedentariness on arterial stiffness and the corresponding risk of CVD.

4.3 | Perspective

A large body of evidence indicates that improving cardiovascular health requires adequate physical activity but also limitation of SB [3, 4]. According to our findings, this paradigm is not reflected in central arterial stiffness whilst it does seem applicable to carotid arterial stiffening. Given the cerebrovascular risks of carotid arterial stiffening [41, 42, 46], SB reduction might be especially effective for reducing the risk of stroke. Longitudinal follow-up studies are needed to disentangle the effects of SB and physical activity on carotid arterial stiffening and the corresponding risk of cerebrovascular diseases and CVD in general. Further research using (compositional) isotemporal substitution modeling to account for the co-dependency of physical behaviors may provide novel insights.

Author Contributions

Conceived and designed research: K.M.v.d.S., E.A.B., T.M.H.E., and D.H.J.T. Performed experiments: K.M.v.d.S., E.A.B., T.P.K., N.A.S., I.A.d.K., J.T., A.E.F.M., P.M.N., and K.V.R. Analyzed data: K.M.v.d.S., E.A.B., T.P.K., and N.A.S. Interpreted results of experiments: K.M.v.d.S., E.A.B., T.M.H.E., and D.H.J.T. Prepared figures: K.M.v.d.S. Drafted manuscript: K.M.v.d.S., E.A.B., T.M.H.E., and D.H.J.T. Edited and revised manuscript: T.P.K., N.A.S., I.A.d.K., J.T., A.E.F.M., K.D.R., P.M.N., K.V.R., and J.J. Approved final version of manuscript: all authors.

Acknowledgments

The authors sincerely thank all individuals who participated in the study and all personnel involved in the data collection.

Members of the Nijmegen Exercise Study collaboration: Neeltje A.E. Allard, Kristian Berge, Coen C.W.G. Bongers, Calvin G. Brouwer, Yvonne A.W. Hartman, Lotte R. Hazeleger, Maria T.E. Hopman, Sylvan L.J.E. Janssen, Jules M. Janssen Daalen, Bregina T.P. Kersten, Lotte Koopmans, Sophie H. Kroesen, Thijs R.J. Landman, Tom T.J. Luiken, Isa H. Mast, Mandy A.G. Peggen, Merle C.A. Schoofs, Bibi A. Schreurs, Jenke J.M. Vermeulen, Janneke I.A. Vloet, and Lisa Wanders. Neeltje A.E. Allard, Kristian Berge, Coen C.W.G. Bongers, Calvin G. Brouwer, Yvonne A.W. Hartman, Lotte R. Hazeleger, Maria T.E. Hopman, Sylvan L.J.E. Janssen, Jules M. Janssen Daalen, Bregina T.P. Kersten, Lotte Koopmans, Sophie H. Kroesen, Thijs R.J. Landman, Tom T.J. Luiken, Isa H. Mast, Mandy A.G. Peggen, Merle C.A. Schoofs, Bibi A. Schreurs, Jenke J.M. Vermeulen, Janneke I.A. Vloet, Lisa Wanders,

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. A. Biswas, P. I. Oh, G. E. Faulkner, et al., "Sedentary Time and Its Association With Risk for Disease Incidence, Mortality, and Hospitalization

in Adults: A Systematic Review and Meta-Analysis," *Annals of Internal Medicine* 162, no. 2 (2015): 123–132, <https://doi.org/10.7326/m14-1651>.

2. R. Patterson, E. McNamara, M. Tainio, et al., "Sedentary Behaviour and Risk of All-Cause, Cardiovascular and Cancer Mortality, and Incident Type 2 Diabetes: A Systematic Review and Dose Response Meta-Analysis," *European Journal of Epidemiology* 33, no. 9 (2018): 811–829, <https://doi.org/10.1007/s10654-018-0380-1>.

3. E. Stamatakis, J. Gale, A. Bauman, U. Ekelund, M. Hamer, and D. Ding, "Sitting Time, Physical Activity, and Risk of Mortality in Adults," *Journal of the American College of Cardiology* 73, no. 16 (2019): 2062–2072, <https://doi.org/10.1016/j.jacc.2019.02.031>.

4. U. Ekelund, J. Tarp, J. Steene-Johannessen, et al., "Dose-Response Associations Between Accelerometry Measured Physical Activity and Sedentary Time and All Cause Mortality: Systematic Review and Harmonised Meta-Analysis," *BMJ* 366 (2019): 14570, <https://doi.org/10.1136/bmj.l4570>.

5. F. C. Bull, S. S. Al-Ansari, S. Biddle, et al., "World Health Organization 2020 Guidelines on Physical Activity and Sedentary Behaviour," *British Journal of Sports Medicine* 54, no. 24 (2020): 1451–1462, <https://doi.org/10.1136/bjsports-2020-102955>.

6. J. A. Chirinos, P. Segers, T. Hughes, and R. Townsend, "Large-Artery Stiffness in Health and Disease," *Journal of the American College of Cardiology* 74, no. 9 (2019): 1237–1263, <https://doi.org/10.1016/j.jacc.2019.07.012>.

7. C. Vlachopoulos, K. Aznaouridis, and C. Stefanadis, "Prediction of Cardiovascular Events and All-Cause Mortality With Arterial Stiffness," *Journal of the American College of Cardiology* 55, no. 13 (2010): 1318–1327, <https://doi.org/10.1016/j.jacc.2009.10.061>.

8. Y. Ben-Shlomo, M. Spears, C. Boustred, et al., "Aortic Pulse Wave Velocity Improves Cardiovascular Event Prediction," *Journal of the American College of Cardiology* 63, no. 7 (2014): 636–646, <https://doi.org/10.1016/j.jacc.2013.09.063>.

9. A. Saz-Lara, R. M. Bruno, I. Cavero-Redondo, C. Álvarez-Bueno, B. Notario-Pacheco, and V. Martínez-Vizcaíno, "Association Between Arterial Stiffness and Blood Pressure Progression With Incident Hypertension: A Systematic Review and Meta-Analysis," *Frontiers in Cardiovascular Medicine* 9 (2022): 798934, <https://doi.org/10.3389/fcvm.2022.798934>.

10. S. Carter, Y. Hartman, S. Holder, D. H. Thijssen, and N. D. Hopkins, "Sedentary Behavior and Cardiovascular Disease Risk: Mediating Mechanisms," *Exercise and Sport Sciences Reviews* 45, no. 2 (2017): 80–86.

11. A. J. Pinto, A. Bergouignan, P. C. Dempsey, et al., "Physiology of Sedentary Behavior," *Physiological Reviews* 103, no. 4 (2023): 2561–2622, <https://doi.org/10.1152/physrev.00022.2022>.

12. I. B. Wilkinson, A. Qasem, C. M. McEniery, D. J. Webb, A. P. Avolio, and J. R. Cockcroft, "Nitric Oxide Regulates Local Arterial Distensibility In Vivo," *Circulation* 105, no. 2 (2002): 213–217, <https://doi.org/10.1161/hc0202.101970>.

13. A. H. Germano-Soares, A. Andrade-Lima, A. L. Meneses, et al., "Association of Time Spent in Physical Activities and Sedentary Behaviors With Carotid-Femoral Pulse Wave Velocity: A Systematic Review and Meta-Analysis," *Atherosclerosis* 269 (2018): 211–218, <https://doi.org/10.1016/j.atherosclerosis.2018.01.009>.

14. S. Kozey-Keadle, A. Libertine, K. Lyden, J. Staudenmayer, and P. S. Freedson, "Validation of Wearable Monitors for Assessing Sedentary Behavior," *Medicine & Science in Sports & Exercise* 43, no. 8 (2011): 1561–1567.

15. K. Lyden, S. L. Kozey Keadle, J. W. Staudenmayer, and P. S. Freedson, "Validity of Two Wearable Monitors to Estimate Breaks From Sedentary Time," *Medicine & Science in Sports & Exercise* 44, no. 11 (2012): 2243–2252.

16. M. F. H. Maessen, A. L. M. Verbeek, E. A. Bakker, P. D. Thompson, M. T. E. Hopman, and T. M. H. Eijssvogels, "Lifelong Exercise Patterns and Cardiovascular Health," *Mayo Clinic Proceedings* 91, no. 6 (2016): 745–754, <https://doi.org/10.1016/j.mayocp.2016.02.028>.
17. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), "Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report," *Circulation* 106, no. 25 (2002): 3143–3421.
18. American Diabetes Association, "2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2018," *Diabetes Care* 41, no. 1 (2017): S13–S27, <https://doi.org/10.2337/dc18-S002>.
19. E. A. Winkler, D. H. Bodicoat, G. N. Healy, et al., "Identifying adults' Valid Waking Wear Time by Automated Estimation in ActivPAL Data Collected With a 24 h Wear Protocol," *Physiological Measurement* 37, no. 10 (2016): 1653–1668, <https://doi.org/10.1088/0967-3334/37/10/1653>.
20. E. A. Bakker, B. M. A. Van Bakel, W. R. M. Aengevaeren, et al., "Sedentary Behaviour in Cardiovascular Disease Patients: Risk Group Identification and the Impact of Cardiac Rehabilitation," *International Journal of Cardiology* 326 (2021): 194–201, <https://doi.org/10.1016/j.ijcard.2020.11.014>.
21. P. M. Nabeel, K. V. Raj, and J. Joseph, "Image-Free Ultrasound for Local and Regional Vascular Stiffness Assessment: The ARTSENS Plus," *Journal of Hypertension* 40, no. 8 (2022): 1537–1544, <https://doi.org/10.1097/HJH.0000000000003181>.
22. L. M. Van Bortel, S. Laurent, P. Boutouyrie, et al., "Expert Consensus Document on the Measurement of Aortic Stiffness in Daily Practice Using Carotid-Femoral Pulse Wave Velocity," *Journal of Hypertension* 30, no. 3 (2012): 445–448, <https://doi.org/10.1097/hjh.0b013e32834fa8b0>.
23. M. E. Boesen, D. Singh, B. K. Menon, and R. Frayne, "A Systematic Literature Review of the Effect of Carotid Atherosclerosis on Local Vessel Stiffness and Elasticity," *Atherosclerosis* 243, no. 1 (2015): 211–222, <https://doi.org/10.1016/j.atherosclerosis.2015.09.008>.
24. K. Hayashi, T. Yamamoto, A. Takahara, and K. Shirai, "Clinical Assessment of Arterial Stiffness With Cardio-Ankle Vascular Index: Theory and Applications," *Journal of Hypertension* 33, no. 9 (2015): 1742–1757, <https://doi.org/10.1097/hjh.0000000000000651>.
25. S. Laurent, J. Cockcroft, L. Van Bortel, et al., "Expert Consensus Document on Arterial Stiffness: Methodological Issues and Clinical Applications," *European Heart Journal* 27, no. 21 (2006): 2588–2605, <https://doi.org/10.1093/eurheartj/ehl254>.
26. P. M. Nabeel, V. R. Kiran, J. Joseph, V. V. Abhidev, and M. Sivaprakasam, "Local Pulse Wave Velocity: Theory, Methods, Advancements, and Clinical Applications," *IEEE Reviews in Biomedical Engineering* 13 (2020): 74–112, <https://doi.org/10.1109/rbme.2019.2931587>.
27. I. B. Wilkinson, C. M. McEnery, G. Schillaci, et al., "ARTERY Society Guidelines for Validation of Non-Invasive Haemodynamic Measurement Devices: Part 1, Arterial Pulse Wave Velocity," *Artery Research* 4, no. 2 (2010): 34, <https://doi.org/10.1016/j.artres.2010.03.001>.
28. C. Andersson, A. Lyass, M. G. Larson, et al., "Physical Activity Measured by Accelerometry and Its Associations With Cardiac Structure and Vascular Function in Young and Middle-Aged Adults," *Journal of the American Heart Association* 4, no. 3 (2015): e001528, <https://doi.org/10.1161/jaha.114.001528>.
29. A. M. Gerage, T. R. B. Benedetti, B. Q. Farah, et al., "Sedentary Behavior and Light Physical Activity Are Associated With Brachial and Central Blood Pressure in Hypertensive Patients," *PLoS One* 10, no. 12 (2015): e0146078, <https://doi.org/10.1371/journal.pone.0146078>.
30. M. A. Gomez-Marcos, J. I. Recio-Rodríguez, M. C. Patino-Alonso, et al., "Relationship Between Objectively Measured Physical Activity and Vascular Structure and Function in Adults," *Atherosclerosis* 234, no. 2 (2014): 366–372, <https://doi.org/10.1016/j.atherosclerosis.2014.02.028>.
31. T. J. Parsons, C. Sartini, E. A. Ellins, et al., "Objectively Measured Physical Activity, Sedentary Time and Subclinical Vascular Disease: Cross-Sectional Study in Older British Men," *Preventive Medicine* 89 (2016): 194–199, <https://doi.org/10.1016/j.ypmed.2016.05.031>.
32. Y. Gando, K. Yamamoto, H. Murakami, et al., "Longer Time Spent in Light Physical Activity Is Associated With Reduced Arterial Stiffness in Older Adults," *Hypertension* 56, no. 3 (2010): 540–546, <https://doi.org/10.1161/hypertensionaha.110.156331>.
33. L. Bohn, A. Ramoa, G. Silva, et al., "Sedentary Behavior and Arterial Stiffness in Adults With and Without Metabolic Syndrome," *International Journal of Sports Medicine* 38, no. 05 (2017): 396–401, <https://doi.org/10.1055/s-0043-101676>.
34. B. L. Horta, B. D. Schaan, R. M. Bielemann, et al., "Objectively Measured Physical Activity and Sedentary-Time Are Associated With Arterial Stiffness in Brazilian Young Adults," *Atherosclerosis* 243, no. 1 (2015): 148–154, <https://doi.org/10.1016/j.atherosclerosis.2015.09.005>.
35. Q. L. Huynh, C. L. Blizzard, J. E. Sharman, C. G. Magnussen, T. Dwyer, and A. J. Venn, "The Cross-Sectional Association of Sitting Time With Carotid Artery Stiffness in Young Adults," *BMJ Open* 4, no. 3 (2014): e004384, <https://doi.org/10.1136/bmjopen-2013-004384>.
36. T. Tarumi, M. M. Gonzales, B. Fallow, et al., "Central Artery Stiffness, Neuropsychological Function, and Cerebral Perfusion in Sedentary and Endurance-Trained Middle-Aged Adults," *Journal of Hypertension* 31, no. 12 (2013): 2400–2409.
37. M. Motohiko, "Effects of Resistance Training on Arterial Stiffness: A Meta-Analysis," *British Journal of Sports Medicine* 47, no. 6 (2013): 393–396, <https://doi.org/10.1136/bjsports-2012-090488>.
38. S. J. Vermeersch, E. R. Rietzschel, M. L. De Buyzere, et al., "Age and Gender Related Patterns in Carotid-Femoral PWV and Carotid and Femoral Stiffness in a Large Healthy, Middle-Aged Population," *Journal of Hypertension* 26, no. 7 (2008): 1411–1419.
39. A. Paini, P. Boutouyrie, D. Calvet, A.-I. Tropeano, B. Laloux, and S. P. Laurent, "Carotid and Aortic Stiffness," *Hypertension* 47, no. 3 (2006): 371–376, <https://doi.org/10.1161/01.hyp.0000202052.25238.68>.
40. P. Salvi, F. Valbusa, A. Kearney-Schwartz, et al., "Non-Invasive Assessment of Arterial Stiffness: Pulse Wave Velocity, Pulse Wave Analysis and Carotid Cross-Sectional Distensibility: Comparison Between Methods," *Journal of Clinical Medicine* 11, no. 8 (2022): 2225, <https://doi.org/10.3390/jcm11082225>.
41. T. T. van Sloten, M. T. Schram, K. van den Hurk, et al., "Local Stiffness of the Carotid and Femoral Artery Is Associated With Incident Cardiovascular Events and All-Cause Mortality: The Hoorn Study," *Journal of the American College of Cardiology* 63, no. 17 (2014): 1739–1747, <https://doi.org/10.1016/j.jacc.2013.12.041>.
42. T. T. Van Sloten, S. Sedaghat, S. Laurent, et al., "Carotid Stiffness Is Associated With Incident Stroke," *Journal of the American College of Cardiology* 66, no. 19 (2015): 2116–2125, <https://doi.org/10.1016/j.jacc.2015.08.888>.
43. J. A. H. R. Claassen, D. H. J. Thijssen, R. B. Panerai, and F. M. Faraci, "Regulation of Cerebral Blood Flow in Humans: Physiology and Clinical Implications of Autoregulation," *Physiological Reviews* 101, no. 4 (2021): 1487–1559, <https://doi.org/10.1152/physrev.00022.2020>.
44. S. E. Carter, R. Draijer, S. M. Holder, L. Brown, D. H. J. Thijssen, and N. D. Hopkins, "Regular Walking Breaks Prevent the Decline in Cerebral Blood Flow Associated With Prolonged Sitting," *Journal of Applied Physiology* 125, no. 3 (2018): 790–798, <https://doi.org/10.1152/jappphysiol.00310.2018>.

45. I. D. Braz and J. P. Fisher, "The Impact of Age on Cerebral Perfusion, Oxygenation and Metabolism During Exercise in Humans," *Journal of Physiology* 594, no. 16 (2016): 4471–4483, <https://doi.org/10.1113/JP271081>.

46. E. Y. Yang, L. Chambless, A. R. Sharrett, et al., "Carotid Arterial Wall Characteristics Are Associated With Incident Ischemic Stroke but Not Coronary Heart Disease in the Atherosclerosis Risk in Communities (ARIC) Study," *Stroke* 43, no. 1 (2012): 103–108, <https://doi.org/10.1161/strokeaha.111.626200>.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.