

Habitual Physical Activity and Peripheral Arterial Compliance in Young Adults: The Amsterdam Growth and Health Longitudinal Study

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BACKGROUND

It remains unclear whether the impact of habitual physical activity (HPA) differs for central vs. peripheral arterial stiffness, both of which are detrimental to cardiovascular health. We investigated the associations of lifetime HPA of different intensities on brachial and femoral stiffness in young adults, and compared these with those previously obtained for the carotid artery in the same study population.

METHODS

Prospectively measured data (eight repeated measures between ages 13 and 36 years) on HPAs, and other lifestyle and biological variables, were retrieved for 373 subjects in whom stiffness of the brachial and femoral, as well as the carotid, arteries was assessed at age 36 years. Generalized estimating equations were used to examine the differences in time spent in HPAs (min/week) across sex-specific tertiles of the brachial and femoral distensibility (DC) and compliance (CC) coefficients.

RESULTS

After adjustment for potential confounders, subjects in the highest (more compliant) vs. those in the lowest tertiles of the

brachial and femoral CCs (less compliant) at age 36 years had spent on average more time in vigorous (+21.2 (95%CI:2.0; 40.4) and +24.4 (5.0; 43.8), respectively) but not in light-to-moderate HPAs throughout the longitudinal period. These differences were explained by 28 and 62%, respectively, by vigorous-HPA-related favorable impacts on other cardiovascular risk factors. No such associations were observed for the brachial and femoral DCs, however.

CONCLUSIONS

Lifetime vigorous, but not light-to-moderate, HPA is favorably associated with brachial and femoral compliance, but not DC. Altogether, these and our previous findings thus suggest generalized vigorous-HPA-related adaptations, although of different nature, throughout the arterial tree.

Keywords: adolescence; arterial stiffness; blood pressure; epidemiology; habitual physical activity; hypertension; life-course; lifestyle; risk factors; young adults

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Arterial stiffness is a major risk factor for the development of cardiovascular disease.¹ Its predictive value for cardiovascular risk has yet only been established for central (i.e. elastic) arteries,¹ but higher stiffness levels of peripheral (i.e. muscular) arteries may also be detrimental to cardiovascular health. Indeed, stiffening of the more distal part of the arterial tree may boost the premature return of the reflected pulse wave

at the level of the ascending aorta, thereby increasing cardiac afterload during the systolic phase of the cardiac cycle.² In addition, although complications related to arterial stiffness, such as left ventricular hypertrophy, stroke, and myocardial infarction, in general occur later in life, the development of arterial stiffening is rooted in childhood/adolescence and is characterized by a preclinical and asymptomatic phase that lasts for many decades.³⁻⁵ Taking all this together, identifying modifiable risk factors among the young that contribute to stiffening of not only the central, but also of the peripheral arteries is, thus, of great importance as it may enable a better understanding of the cross-talk between proximal and distal parts of the arterial tree⁶ and may help to construct targeted prevention strategies with the most potential for health benefits later in life.

Higher levels of habitual physical activity (HPA) are favorably associated with arterial stiffness,⁷ which might explain the HPA-related lower risk of incident hypertension among

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apparently healthy adult men.⁸ However, whether such beneficial associations with arterial stiffness differ between central and peripheral arteries is not clear. The interpretation of the literature with this regard is hampered because most of the studies so far have investigated the association between HPA and stiffness estimates of one artery or arterial segment only, most often the carotid distensibility (DC) or compliance (CC) coefficients or the aortic pulse-wave velocity.^{9–23} The few studies that have investigated associations with stiffness of both types of arteries have shown HPA to be inversely associated with stiffness levels of: (i) central arteries only,²⁴ arguing in favor of adaptations of mainly the elastic part of the arterial tree; (ii) peripheral arteries only,²⁵ arguing in favor of a localized adaptation of the arteries irrigating the limbs directly involved with exercise; or (iii) both types of arteries,^{26,27} arguing in favor of a “generalized effect” of HPA.

We have recently shown, in the Amsterdam Growth and Health Longitudinal Study (AGAHLS), that young adults with stiffer vs. those with less-stiff carotid arteries had spent less time in vigorous, but not in light-to-moderate, intensity HPA throughout the course of their lives, i.e. from adolescence to adulthood, suggesting a favorable impact of this type of HPA on central arterial stiffness.²⁸ This favorable association was explained, into a great extent, by vigorous-HPA-related beneficial associations with traditional cardiovascular risk factors. A major strength of the AGAHLS is that subjects’ HPAs and other cardiovascular risk factors were assessed prospectively throughout their lives, which enables the investigation of “lifetime exposure” to HPAs in relation to subjects’ arterial stiffness levels in adulthood. This is in contrast to the previous studies mentioned above, which have ascertained subjects’ HPA status on the basis of cross-sectional or retrospective examinations. In addition, arterial properties were assessed not only in the carotid, but also the brachial and femoral arteries, which allows us to comprehensively examine whether our previous findings are confined to the central carotid artery or also hold true for the peripheral arteries.

In view of these considerations, we have investigated (i) the extent to which the mean levels of HPAs, of light-to-moderate and/or vigorous intensity, performed from adolescence up to adulthood differed between subjects with stiffer vs. those with less stiff brachial and femoral arteries at the age of 36 years; and (ii) the extent to which any such differences could be explained by the favorable association between lifetime HPAs and other biological cardiovascular risk factors.²⁸

METHODS

Subjects and study design. All subjects were participants of the AGAHLS. This study started in 1977 with a group of ~600 boys and girls from two secondary schools in the Netherlands.²⁹ The mean age of the subjects at the beginning of the study was 13.1 (s.d. 0.8) years. Since then, measurements were obtained 2–8 times (i.e., at the ages of 13, 14, 15, 16, 21, 27, 32, and 36 years) during a 24-year follow-up period. At each measurement, anthropometrical, biological, and lifestyle variables were assessed. In 2000, when subjects’ mean age was 36.5 (s.d. 0.6)

years, properties of the carotid, brachial, and femoral arteries were assessed for the first time in 377 subjects.^{28,30,31} This study reports on 373 of these subjects (196 women) in whom complete data on all three arteries were available.

The study was approved by the medical ethical committee of the VU University Medical Center (Amsterdam, the Netherlands), and all subjects gave their written informed consent (provided by their parents when subjects were 13–16 years old).

Arterial stiffness. When subjects were 36 years old, properties of three large arteries were assessed by means of noninvasive ultrasonography according to guidelines for user procedures and with the use of reproducible methods and devices.^{1,32,33} All subjects had abstained from smoking and caffeine-containing beverages on the day the measurements were performed. Measurements took place after subjects had been resting in a supine position for 15 min in a quiet temperature-controlled room. Properties of the right brachial (20 mm above the antecubital fossa) and the common femoral (20 mm proximal to the flow divider) arteries were obtained by two trained vascular sonographers with the use of an ultrasound scanner equipped with a 7.5-MHz linear array probe (Pie Medical, Maastricht, the Netherlands). The ultrasound scanner was connected to a personal computer equipped with an acquisition system and a vessel wall movement detector software system (Wall Track System 2; Pie Medical). This integrated device enabled measurements of arterial diameter (D) and distension (ΔD) as described in detail elsewhere.

Throughout the entire period of ultrasound imaging, systolic, diastolic, and mean arterial blood pressure were assessed in the left arm at 5-min intervals with an oscillometric device (Colin Press-Mate, model BP-8800, Komaki City, Japan). Brachial artery pulse pressure (PP) was defined as systolic – diastolic pressure, and PP at the level of the femoral artery was calculated by calibration of the distension waveforms.³⁴ The mean brachial and femoral D , ΔD , and local PP of three consecutive measurements (each including 3–7 heart beats) were used to estimate the DC and CC as follows^{30,31}:

$$DC = (2\Delta D \cdot D + \Delta D^2) / (PP \cdot D^2) \quad \text{in } 10^{-3} / \text{kPa} \quad (1)$$

$$CC = \pi(2D \cdot \Delta D + \Delta D^2) / 4PP \quad \text{in } \text{mm}^2 / \text{kPa} \quad (2)$$

HPA. HPA was measured at each measurement occasion (i.e., from age 13 to 36 years) by means of a structured detailed face-to-face interview.²⁸ At the mean ages of 27 and 32 years, a standard form containing cues was used during the HPA interview, and, at the mean age of 36 years, an identical interviewer-administered computer-assisted version was introduced. The intensity, frequency, and duration of all physical activities (at school, at work, at home, during leisure time, organized and unorganized sports, climbing stairs, and active transportation) with a duration of at least 5 min and exceeding an intensity level of four times the resting metabolic rate (i.e., >4 meta-

bolic equivalents) were retrieved. According to their intensities, activities were then classified into light-to-moderate (4–7 metabolic equivalents, e.g., brisk walking), hard (7–10 metabolic equivalents, e.g., tennis, jogging), and very hard (>10 metabolic equivalents, e.g., squash). Extreme values of HPA at given time points, i.e., those above 3 s.d. from the time-specific mean level, were excluded from the analyses, and time spent in hard and very hard intensity HPAs were combined into a “vigorous” intensity category.²⁸

Covariates. Throughout the 24-year study period other lifestyle (i.e., alcohol consumption, smoking behavior, and dietary intake), anthropometrical (i.e., body height, body weight, body skinfolds, and skinfolds ratio), and biological (i.e., sitting blood pressure, cardiorespiratory fitness, blood lipids, and resting heart rate) risk factors were measured as described in detail elsewhere.^{29–31,35}

Statistical analyses. We used generalized estimating equations to investigate the mean differences in time spent in light-to-moderate and vigorous-intensity HPAs throughout the 24-year longitudinal period (i.e., from age 13 to 36 years), between subjects in the middle (T2) and highest (T3) vs. those in the lowest sex-specific tertiles (T1) of the brachial and femoral DC and

CC at the age of 36 years. Note that higher levels of both the DC and CC represent lower levels of arterial stiffness. The method of longitudinal data analyses adopted adjusts for the correlation between repeated observations taken in the same subject and has the advantage of handling repeated data of subjects with varying numbers and unequally time-spaced observations.³⁶ The analyses were first adjusted for sex, body height, and time (model 1), and subsequently for other lifestyle risk factors (i.e., smoking and alcohol drinking statuses (yes/no), and total energy intake (in kilocalories per day)), all considered as potential confounders (model 2). Next, we further adjusted for other biological cardiovascular risk factors (i.e., mean arterial pressure, skinfolds ratio, cardiorespiratory fitness, total-to-high-density lipoprotein cholesterol ratio, and resting heart rate), all considered as potential mediators, to ascertain the extent to which any differences in HPAs between the groups being compared could be explained by favorable associations between HPAs and these risk factors (models 3a to 3e and 4).²⁸

In addition, we examined the trajectories of the different intensity HPAs, from age 13 to 36 years, between the groups being compared by adding interaction terms between groups and time to model 1 described above. Results hereby obtained were displayed graphically (smoothed line plots).^{28,35}

Table 1 | Characteristics of the study population throughout the 24-year longitudinal period

Variables	Calendar age (years)							
	13	14	15	16	21	27	32	36
Habitual physical activity								
Total, min/week	579 ± 192	548 ± 197	548 ± 226	516 ± 198	513 ± 299	452 ± 313	499 ± 303	745 ± 455
Light-to-moderate, min/week	281 ± 142	310 ± 159	375 ± 196	366 ± 182	427 ± 269	354 ± 305	369 ± 268	628 ± 449
Vigorous, min/week	298 ± 160	237 ± 125	172 ± 103	150 ± 97	85 ± 114	98 ± 94	130 ± 138	117 ± 99
Other lifestyle risk factors								
Alcohol consumption, %	13.5	15.9	33.3	48.2	69.0	72.5	80.3	82.1
Smoking, %	1.6	11.0	14.0	17.9	29.9	26.2	20.2	23.5
Total energy intake, 1,000 kcal/day	2.46 ± 0.55	2.51 ± 0.59	2.59 ± 0.68	2.55 ± 0.68	2.62 ± 0.73	2.48 ± 0.64	2.60 ± 0.71	2.62 ± 0.70
Biological risk factors								
Mean arterial pressure, mm Hg	91.9 ± 6.9	91.7 ± 6.6	90.1 ± 6.6	91.8 ± 7.2	95.4 ± 8.0	97.2 ± 8.4	99.6 ± 9.0	100.7 ± 11.0
Body mass index, kg/m ²	17.7 ± 1.8	18.4 ± 2.0	19.2 ± 2.1	19.8 ± 2.1	21.4 ± 2.2	22.2 ± 2.3	23.3 ± 2.9	24.1 ± 3.1
Sum of four skinfolds, ^a mm	32.0 ± 12.0	33.5 ± 14.0	35.3 ± 15.0	38.9 ± 16.6	44.8 ± 17.2	41.9 ± 16.1	47.4 ± 19.2	51.5 ± 18.2
Skinfold ratio ^b	0.49 ± 0.06	0.51 ± 0.06	0.53 ± 0.06	0.55 ± 0.06	0.58 ± 0.08	0.56 ± 0.08	0.56 ± 0.09	0.57 ± 0.10
VO _{2max} , ml/min/kg ^{FFM}	69.5 ± 6.5	68.9 ± 6.3	67.0 ± 5.7	66.2 ± 6.5	59.8 ± 6.2	56.6 ± 6.4	56.5 ± 7.4	60.6 ± 8.4
Total-to-HDL cholesterol ratio	3.2 ± 0.7	3.2 ± 0.7	3.4 ± 0.8	3.2 ± 0.7	3.8 ± 0.9	3.8 ± 1.0	3.7 ± 1.2	3.8 ± 1.3
Resting heart rate, bpm	83 ± 14	79 ± 13	79 ± 15	76 ± 14	72 ± 13	72 ± 13	75 ± 14	71 ± 11

Data are means ± s.d. or percentages.

bpm, beats per minute; FFM, fat-free mass; HDL, high-density lipoprotein.

^aSum of the thickness of the following skinfolds: triceps, biceps, subscapular, and suprailiac. ^bRatio calculated as: (subscapular + suprailiac)/sum of four skinfolds.

In all generalized estimating equation analyses, an exchangeable correlation structure was used, which was deemed the most appropriate after examination of the interperiod correlation matrix of HPA throughout the 24-year study period. All results are reported for men and women combined as no significant interactions with sex were found. All statistical analyses were performed with the use of the STATA software package, version 9.2 (StataCorp, College Station, TX).

RESULTS

Table 1 presents study participants’ characteristics at the different ages throughout the longitudinal period. The mean levels of the DC and the CC of the brachial and femoral arteries across tertiles of each stiffness estimate are shown in Table 2.

Lifetime light-to-moderate and vigorous-intensity HPA and brachial and femoral stiffness in young adulthood
Compared to subjects in T1 (i.e., with stiffer), those in T2 and T3 (i.e., with less-stiff arteries) of the brachial CC at age 36 years had spent increasingly more time in vigorous (+14.9 min/week (95%CI: -4.9 to 34.6) and +23.4 min/week (3.7 to 43.2), respectively), but not in light-to-moderate HPAs (+20.8 min/week (-20.6 to 62.2) and -6.9 min/week (-48.3 to 34.5), respectively) throughout the longitudinal period. Similarly, compared to subjects in T1, those in T2 and T3 of the femoral CC at age 36 had spent increasingly more time in vigorous (+11.8 min/week (-8.1 to 31.7) and +25.3 min/week (5.2-45.3), respectively), but not in light-to-moderate HPAs (-17.2 min/week (-58.8 to 24.3) and -12.9 min/week (-54.8 to 29.0), respectively) throughout the longitudinal period (Figure 1a,b; Table 3, model 1). No

such differences were found across the tertiles of the brachial and femoral DC at age 36 years (Figure 1a,b).
Adjustment for the other lifestyle risk factors, i.e., potential confounders, slightly attenuated the differences in time spent in vigorous-intensity HPA between T3 and T1 of the brachial and femoral CC (to +21.2 min/week (2.0 to 40.4) and +24.4 min/week (5.0 to 43.8), respectively), which nevertheless remained significant (Table 3, model 2). These differences decreased after additional adjustment for skinfolds ratio and cardiorespiratory fitness separately (models 3b and 3c, respectively), but less so by mean arterial pressure, total-to-high-density lipoprotein cholesterol, and resting heart rate (models 3a, 3d, and 3e, respectively). When adjustments accounted for all these

Table 2 Mean levels across tertiles of each brachial and femoral stiffness estimate at the age of 36 years			
Stiffness estimates	T1	T2	T3
Brachial artery			
Distensibility coefficient, 10 ⁻³ /kPa	7.1 ± 2.1	12.4 ± 2.5	24.2 ± 9.4
Compliance coefficient, mm ² /kPa	0.09 ± 0.03	0.15 ± 0.03	0.27 ± 0.08
Femoral artery			
Distensibility coefficient, 10 ⁻³ /kPa	4.0 ± 1.1	6.5 ± 1.2	11.1 ± 4.0
Compliance coefficient, mm ² /kPa	0.29 ± 0.06	0.46 ± 0.05	0.78 ± 0.20

Data are means ± s.d.
T1 (lowest tertile), T2 (middle tertile), and T3 (highest tertile) of each brachial and femoral stiffness estimate.

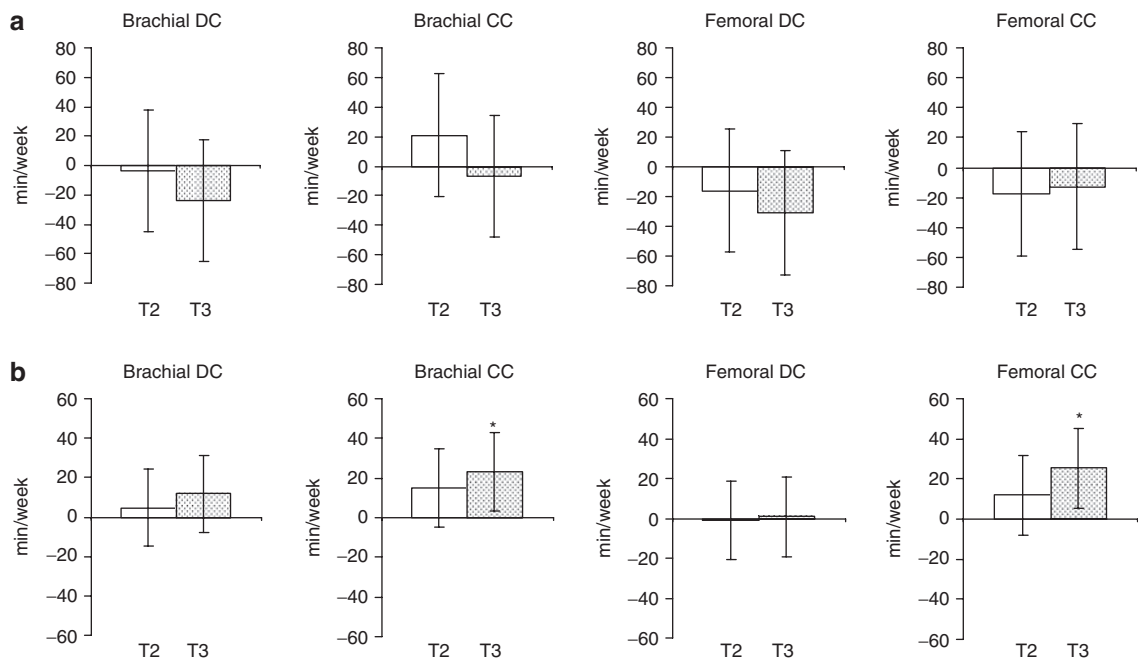


Figure 1 | Mean differences in time spent in (a) light-to-moderate and (b) vigorous-intensity habitual physical activity throughout the 24-year longitudinal period between subjects with increasing levels (tertiles) of the brachial and femoral distensibility (DC) and compliance (CC) coefficients at the age of 36 years. Data are adjusted for sex, height, and time; error bars indicate the 95% confidence interval; **P* < 0.05 for T3 (highest tertile: less stiff) vs. T1 (lowest tertile: stiffer arteries; reference category).

Table 3 | Mean differences in time spent in habitual physical activities throughout the longitudinal period across tertiles of the brachial and femoral compliance coefficients at age 36 years

		Brachial CC				Femoral CC			
		T2 vs. T1		T3 vs. T1		T2 vs. T1		T3 vs. T1	
		β	95% CI	β	95% CI	β	95% CI	β	95% CI
Model	Adjustments								
Light-moderate HPA									
1	Sex, height, time	20.8	−20.6; 62.2	−6.9	−48.3; 34.5	−17.2	−58.8; 24.3	−12.9	−54.8; 29.0
2	Model 1 + other lifestyles ^a	23.6	−17.8; 65.0	−2.9	−44.1; 38.2	−10.0	−51.4; 31.4	−13.7	−55.3; 27.9
Vigorous-intensity HPA									
1	Sex, height, time	14.9	−4.9; 34.6	23.4	3.7; 43.2*	11.8	−8.1; 31.7	25.3	5.2; 45.3*
2	Model 1 + other lifestyles ^a	17.6	−1.6; 36.9	21.2	2.0; 40.4*	14.1	−5.3; 33.4	24.4	5.0; 43.8*
3a	Model 2 + mean arterial pressure	16.9	−2.4; 36.1	20.5	1.3; 39.7*	13.5	−5.8; 32.9	23.3	3.9; 42.8*
3b	Model 2 + skinfolds ratio	13.6	−5.2; 32.5	17.1	−1.7; 35.9	8.4	−10.6; 27.3	18.1	−0.9; 37.2
3c	Model 2 + cardiorespiratory fitness	15.1	−3.2; 33.4	19.0	0.8; 37.2*	12.4	−6.0; 30.9	16.9	−1.6; 35.4
3d	Model 2 + total-to-HDL cholesterol	20.1	0.8; 39.4*	20.1	0.9; 39.4*	13.0	−6.4; 32.4	22.2	2.8; 41.7*
3e	Model 2 + resting heart rate	17.2	−1.5; 36.0	20.2	1.5; 38.8*	11.4	−7.5; 30.3	21.9	2.9; 40.9*
4	Model 2 + all variables in models 3a–3e	13.0	−4.7; 30.7	15.3	−2.3; 32.9	4.3	−13.6; 22.2	9.3	−8.6; 27.2

β indicates the average difference in time spent in habitual physical activity (in min/week) throughout the 24-year longitudinal period between subjects in the middle (T2) and highest (T3) vs. those in the lowest (T1; i.e., with stiffer arteries) tertiles of the brachial and femoral compliance coefficients (CC) at age 36 years.

β , regression coefficient; CI, confidence interval; HDL, high-density lipoprotein; HPA, habitual physical activity.

^aLifestyles considered were alcohol consumption, smoking behavior, and total daily energy intake.

* $P < 0.05$.

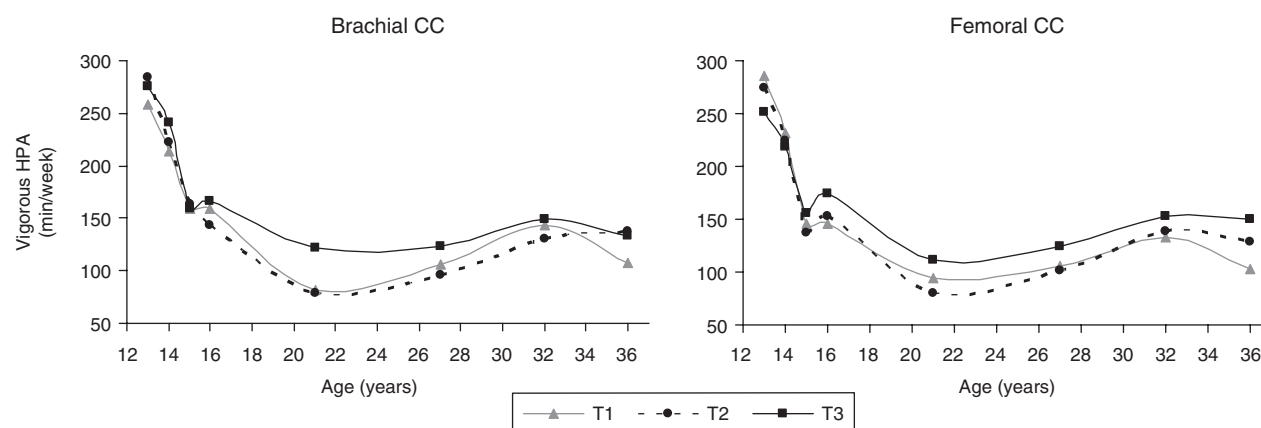


Figure 2 | Trajectories of time spent in vigorous habitual physical activity (HPA) throughout the 24-year longitudinal period by subjects with increasing levels (tertiles) of the brachial and femoral compliance coefficients (CC) at the age of 36 years. Data are adjusted for sex, height, and time. T1, lowest tertile (stiffer); T2, middle tertile; T3, highest tertile (less stiff arteries; reference category).

biological risk factors simultaneously, i.e., potential mediators, the differences in time spent in vigorous HPAs between T3 and T1 of the brachial and femoral CCs were attenuated (i.e., explained) by 28 and 62%, respectively (model 4).

Life-course trajectories of vigorous-intensity HPA across tertiles of the brachial and femoral CC at the age of 36 years

All groups decreased their time spent in vigorous-intensity HPAs throughout the longitudinal period. However, those in T3 of the brachial and femoral CCs at the age of 36 years spent relatively

more time in this intensity of activities, especially from the age of 15 years and thereafter up to the age of 36 years (Figure 2).

Additional analyses

As we found that lifetime vigorous HPA was associated with mainly the CC, but not the DC, of the brachial and the femoral arteries at age 36 years, whereas before we found that vigorous HPA was associated with both the DC and CC of the carotid artery,²⁸ we performed additional analyses to investigate the vigorous-intensity HPA-related differences in driving forces

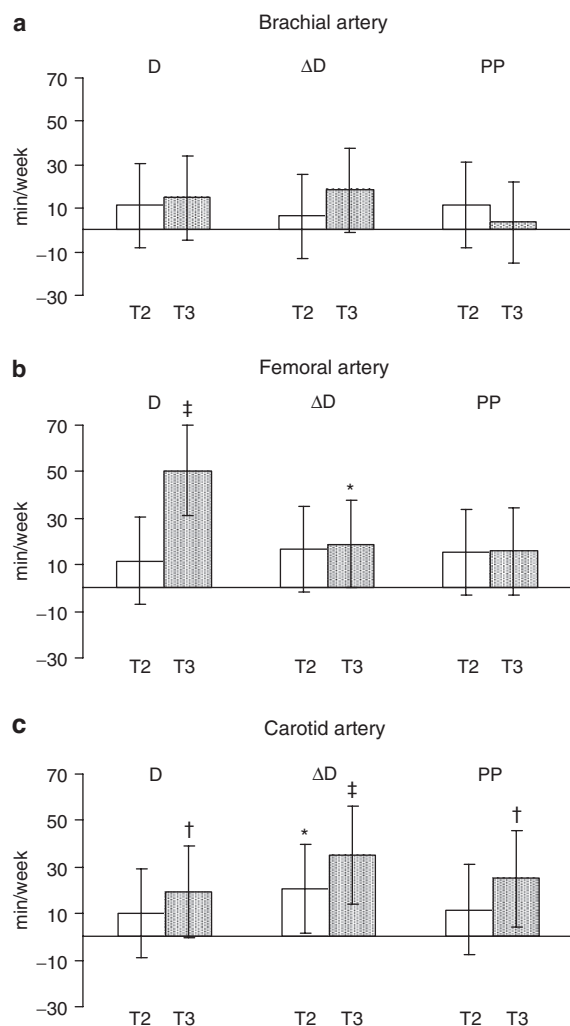


Figure 3 | Mean differences in time spent in vigorous habitual physical activity throughout the 24-year longitudinal period between subjects with increasing levels (tertiles) of the diameter (D), distension (ΔD), and local pulse pressure (PP) of the (a) brachial, (b) femoral, and (c) carotid arteries at the age of 36 years. Data are adjusted for sex, height, time, other lifestyle risk factors, mean arterial pressure, and the other arterial properties as appropriate. Error bars indicate the 95% confidence interval. * $P < 0.05$; $^{\dagger}P < 0.01$; $^{\ddagger}P < 0.001$ for T2 or T3 (higher tertiles) vs. T1 (lowest tertiles; reference category).

(i.e., D, ΔD , or local PP) behind these stiffness estimates in all three arteries (Figure 3). These analyses unveiled a different pattern of associations between lifetime vigorous-intensity HPAs and arterial properties of each artery, such that: in the femoral artery associations were stronger with the arterial diameter (Figure 3b), whereas in the carotid artery associations were stronger with the distension (Figure 3c); strengths of associations with brachial diameter and distension were comparable (Figure 3a). Given that D is positively associated with the CC, but inversely associated with the DC, the above thus explains the differences found between the central carotid and the peripheral femoral arteries.

In addition, and because time spent in light-to-moderate intensity HPAs is inversely associated with time spent in vigorous-intensity HPAs, we have repeated all analyses that

were reported herein with further mutual adjustments for the two types of HPAs. Results of these analyses did not materially differ from the ones reported, however (data not shown).

DISCUSSION

The main findings of this study are threefold: (i) subjects with more compliant, but not distensible, brachial and femoral arteries at age 36 years were characterized by higher levels of vigorous, but not light-to-moderate, intensity HPA between adolescence and adulthood; (ii) this favorable association between vigorous-intensity HPA and brachial and femoral arterial compliance was explained to a great extent by concomitant beneficial associations of this type of HPA with other traditional biological risk factors; and (iii) although all groups decreased their time spent in vigorous-intensity HPA throughout the longitudinal period, subjects with more vs. those with less-compliant brachial and femoral arteries tended to spend relatively more time in this type of HPA from late adolescence and persisted to do so thereafter, up to the age of 36 years.

We recently reported that higher levels of vigorous-intensity HPA performed from adolescence up to adulthood are favorably associated with stiffness levels of the “central” carotid artery in young adulthood²⁸ and now extended these findings by showing favorable lifetime vigorous-HPA-related arterial adaptations in the “peripheral” brachial and femoral arteries. These latter observations are in agreement with previous cross-sectional studies showing that subjects who are more physically active have less-stiff arteries in the upper and/or lower limb,^{14,24–27,37} and intervention studies showing that increases in exercise levels led to decreases in stiffness estimates, in the “long term,” in the arm³⁸ and leg³⁹ arteries. Inconclusive findings in other studies may have been due to lack of power given the low number of study participants,^{40–42} the low intensity of physical activities performed,⁴³ and the participants’ advanced stage of cardiovascular disease.⁴¹

Cardiovascular risk factors may impact differently on arterial stiffness at different localizations throughout the arterial tree.² This might be attributed to the marked difference in architecture of the central vs. peripheral arteries. Indeed, although central arteries contain mainly elastin fibers, and relatively less collagen, this ratio is reversed in the peripheral muscular arteries, where collagen predominates.² Although we found favorable associations of vigorous-intensity HPA with stiffness estimates of all arteries investigated, supporting the view of a generalized effect of exercise throughout the arterial tree,⁴⁴ this seemed to be rooted on different adaptations in the carotid vs. the brachial and femoral arteries. Lifetime vigorous-intensity HPA was associated with greater brachial and femoral CC only, whereas in the carotid artery it was associated with greater DC and CC, as well as with lower β -stiffness index and Young’s elastic modulus.²⁸ The CC reflects the buffering capacity of an artery, and depends more strongly on arterial diameter than on distension. In fact, we found vigorous-HPA-related adaptations toward greater arterial diameter in the femoral artery mainly, which may reflect a relatively greater involvement of leg musculature in the vigorous HPAs reported. Indeed, blood

flow to the peripheral tissues increases during HPA to support the increased metabolic need in the active muscle tissues⁴⁵ and yields arterial remodeling (i.e., larger vessel diameter) in order to restore basal shear stress, a phenomenon that was shown to be endothelium dependent.⁴⁶ Interestingly, our data suggest that vigorous-HPA-related higher levels of the carotid DC and CC were driven by comparatively stronger associations with distension than with diameter, and these occurred despite the also positive association with local PP. We can only speculate that this positive association with PP is due to an increased stroke volume in subjects who spent more time in this type of activity,⁴⁷ rather than an increase in early return of wave reflections, deemed not likely especially in young and apparently healthy subjects as examined herein. Measures of these two factors were not obtained, however. The role of vigorous-intensity HPA on stiffness levels of the central and of the peripheral part of the arterial tree throughout life, the latter of which seems to be comparatively less affected by ageing,^{48,49} needs to be further elucidated in future studies.

By adopting a life-course approach, we were able to identify late adolescence as the period in life during which performance of specifically vigorous-intensity HPA was critical for the peripheral, as well as the central,²⁸ arterial stiffness phenotype several years later in young adulthood. These data are in line with previous studies showing that biological risk factors, such as body fatness, high blood pressure, and dyslipidemia^{4,50–52} at younger ages are associated with arterial stiffness levels in adulthood. In fact, a great extent of the favorable association of lifetime vigorous HPAs with brachial and femoral compliance, as well as with carotid stiffness levels,²⁸ could be explained (i.e. mediated) by concomitant beneficial associations between vigorous HPA and such biological risk factors.

Importantly, the average differences in time spent in vigorous-intensity HPA throughout the longitudinal period between subjects with more vs. those with less compliant peripheral arteries, as well as those with stiffer vs. those with less stiff carotid arteries,²⁸ were relatively small, amounting ~20–25 min/week (or ~3–4 min/day). This thus suggests that even modest increases in this type of HPA, in particular when performed from adolescence onward, may yield beneficial arterial adaptations in young adulthood. Although we do not dismiss the value of light-to-moderate HPA, especially in those subjects who are extremely sedentary and usually overweight, our findings further emphasize the importance of promoting vigorous-intensity HPA, rather than simply any HPA, among the healthy young in order to prevent the development of arterial stiffness-related cardiovascular sequelae later in life.

Some study limitations need to be mentioned. First, the analyses were confined to subjects with complete arterial data at the age of 36 years. However, their levels of HPA as well as of other traditional biological cardiovascular risk factors did not differ, at any earlier time point, with those of subjects who dropped out (data not shown), indicating that our findings were not threatened by selection bias. Second, arterial properties were measured at age 36 years only and, therefore, we

cannot rule out that reverse causation may have occurred. Nevertheless, we think this is unlikely because of the preclinical and asymptomatic nature of arterial stiffness, especially in this young cohort. Third, our findings are confined to local arterial stiffness estimates. No measures on regional stiffness (e.g., aortic or limbs pulse-wave velocity) or wave reflection (e.g., augmentation index) were available in this cohort. Fourth, the assessment of brachial and femoral arterial properties using ultrasonography is accompanied with greater measurement error, as compared to that of the carotid artery.³¹ Therefore, misclassification might have occurred into a greater extent when categorizing subjects according to tertiles of stiffness estimates of these arteries. Nevertheless, if present, such misclassification, would thus have led to an underestimation of the differences in vigorous-intensity HPA levels across tertiles of the brachial and femoral stiffness estimates as reported herein. Fifth, HPAs were grouped according to their intensity levels, but not as aerobic vs. resistance exercises, which are known to affect arterial stiffness differently.⁷ However, the relative time spent in the latter category amounted <2% of the total time spent in HPAs and contributed equally to both intensity types of activities and could not have affected our results. Finally, the assessment of HPA by questionnaires is subject to recall and misclassification bias.⁵³ We think that this was nondifferential because, throughout the study period, participants were not aware of their arterial stiffness levels in adulthood. However, some differential misclassification might have occurred, most probably by overreporting of vigorous HPAs by those with unhealthier lifestyles/risk factor profiles. Either way, the differences in time spent in vigorous-intensity HPA between the groups being compared are likely to be underestimated.

This study enabled us to investigate, comprehensively, the associations of lifetime HPAs with the stiffness levels of peripheral (i.e., brachial and femoral) vs. central (i.e., carotid) arteries in young adulthood. We found favorable associations between vigorous but not light-to-moderate HPAs and compliance, but not DC, of peripheral arteries, whereas previously we have shown that these associations also extend to those estimates reflecting the intrinsic elastic properties of the carotid arterial wall. Thus, though generalized, vigorous-HPA-related adaptations in arterial properties differ in nature across the arterial tree. Altogether, our findings suggest that even modest increases in vigorous-intensity HPA from adolescence up to adulthood may prevent arterial stiffness in young adulthood. This emphasizes the importance of promoting this type of activity in particular as a tool to prevent arterial stiffness-related cardiovascular sequelae later in life.

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