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# Impact of age, sex and exercise on brachial and popliteal artery remodelling in humans

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ABSTRACT

*Objective:* To examine the impact of age, sex and exercise on wall thickness and remodelling in the popliteal and brachial arteries.

*Methods:* We compared wall thickness, lumen diameter and wall:lumen ratios in the brachial and popliteal arteries of 15 young (Y, 25.4 ± 0.8 yr; 7 M 8W) and 16 older sedentary (OS, 58.8 ± 1.1 yr; 8 M 8W) subjects, with 12 of the OS group also studied following 12 and 24 weeks exercise training.

*Results:* Wall thickness and lumen diameter were higher in the popliteal than the brachial artery for both groups ($P < 0.05$); wall:lumen ratio was similar between arteries. Comparison of the Y and OS groups revealed no impact on wall thickness, whereas diameter values were higher in OS subjects ($P < 0.05$). Whilst there were no significant differences in wall thickness between men and women in the Y or OS groups, diameter was larger in men than in women for both arteries ($P < 0.05$). After 24 weeks of training the wall thickness of both arteries decreased ($P < 0.01$) and the wall:lumen ratio of the brachial ($P < 0.01$) and the popliteal ($P < 0.05$) decreased.

*Conclusion:* The cross-sectional results suggest that ageing was associated with increased lumen diameter, although wall:lumen ratio remained unchanged. Wall:lumen ratio was higher in women than men, irrespective of subject age or the artery studied. This related primarily to differences in lumen diameter between the sexes, as wall thickness did not significantly differ between men and women. Our longitudinal data strongly suggest that exercise training is associated with beneficial effects on conduit artery wall thickness and wall:lumen ratio in both upper and lower limbs in humans.



## 1. Introduction

In vessels prone to the development of atherosclerosis, such as the carotid arteries, ageing is associated with increased artery wall thickness, which reflects sub-clinical atherosclerosis and predicts cardiovascular events [1–4]. Limited evidence also suggests that wall thickness in atherosclerosis-prone peripheral arteries, such as those in the lower limbs, increases with age [5]. Less is known regarding the impact of age and sex on wall thickness in arteries which do not typically develop atherosclerosis, such as those in the upper limbs. Comparing arteries which are either prone, or less susceptible, to atherogenic change may reveal the degree to which wall thickening reflects physiological age-related remodelling, versus pathophysiological sub-intimal plaque development. In the present study we examined the hypothesis that popliteal artery wall thickness and wall:lumen ratio would change to a greater extent with age than the brachial artery.

Exercise training is associated with increases in conduit and resistance artery diameter which are mediated, at least in part, through episodic increases in wall shear stress which induce endothelium-mediated remodelling [6–10]. Less information is available regarding the impact of exercise on arterial wall thickness and wall:lumen ratio [1,11] and no previous studies, to our knowledge, have directly compared the impact of exercise training on upper versus lower limb conduit arteries. A secondary hypothesis was that exercise training in sedentary older men and women would decrease arterial wall thickness and wall:lumen ratio.

## 2. Methods

### 2.1. Subjects

Fifteen healthy young recreationally active volunteers and 16 older healthy sedentary subjects were recruited from the commu-

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nity (Table 1). No subjects had any history of hypercholesterolemia, hypertension, insulin resistance, or diabetes. Those who smoked, had a family history of premature coronary disease, or were on medications of any type, including oral contraceptives and hormone replacement therapy, were also excluded, as were individuals taking vitamin or any other supplements. All older women were post-menopausal, whilst pre-menopausal females were tested during the early follicular phase of their menstrual cycle. The healthy young subjects were defined as individuals undertaking <3 h of regular exercise per week at a recreational level. The older sedentary group reported undertaking no regular exercise. In the longitudinal study, 12 of the OS group were studied before and after 12 and 24 weeks of an exercise intervention program.

The study was approved by the Liverpool John Moores University ethics committee and subjects provided written informed consent prior to participation. This conformed to the standards set out by the Declaration of Helsinki.

### 2.2. Experimental design

Participants initially attended the laboratory for assessment of brachial and popliteal artery lumen diameter and wall thickness. Those OS subjects in the longitudinal study underwent repeat testing following 12 and 24 weeks of supervised exercise training. All measurements were performed after subjects were requested to fast for 6 h and abstain from caffeine and/or alcohol for 8 h (Table 2). None of the subjects performed any strenuous physical activity for at least 24 h before the test and repeat measures were collected at the same time of day.

### 2.3. Experimental procedures

#### 2.3.1. Conduit artery diameter and wall thickness

A 10 MHz linear array transducer attached to a high-resolution ultrasound machine (Aspen, Acuson; Mountain View, California) was used to assess lumen diameter and wall thickness of the brachial artery in the distal third of the upper arm and the popliteal artery in the popliteal fossa. An experienced and accredited vascular sonographer (M.A.B.) performed all measurements. Clearly demarcated intimal-medial boundaries were provided by perpendicular incidence of the imaging ultrasound beam in relation to the orientation of the vessel. Images were optimised by using contrast controls on the ultrasound machine. Ultrasound parameters were set to optimise longitudinal B-mode images of the lumen/arterial wall interface.

### 2.4. Conduit artery diameter and wall thickness analysis

Brachial and popliteal artery images were analysed using custom-designed edge-detection and wall-tracking software. This DICOM-based software is largely independent of investigator bias and has been previously described in detail [12,13]. Briefly, the initial video signal was encoded and stored as a digital DICOM file on the PC, using an IMAQ-PCI-1407 card. Software analysis was performed at 30 Hz using an icon-based graphical programming language and toolkit (LabView 6.02, National Instruments, Austin, TX). By identifying a region of interest (ROI) on each first frame of every individual study, capturing both walls of the artery, an automated calibration was made of diameters on the B-mode image. Within the identified ROI in the diameter image, a pixel-density algorithm automatically identified the angle-corrected near and far wall e-lines for every pixel column for diameter assessment. The same algorithm was used to identify the far wall media-adventitia interface. Detection of the near and far wall lumen edges and the far wall media-adventitia interface was performed on every frame selected.

**Table 1**
Subject characteristics of healthy young and older sedentary subjects.

| | Young | | Older sedentary | |
|---|---|---|---|---|
| | Men | Women | Men | Women |
| *N* | 7 | 8 | 8 | 8 |
| Age, yr | 25 ± 1 | 26 ± 1 | 59 ± 2† | 59 ± 2† |
| SBP, mmHg | 113 ± 1 | 102 ± 4 | 125 ± 6 | 122 ± 5* |
| DBP, mmHg | 71 ± 4 | 56 ± 3 | 73 ± 3 | 68 ± 3* |
| BMI, kg/m$^2$ | 23 ± 1 | 23 ± 1 | 29 ± 1† | 30 ± 1† |
| Body fat (DEXA), % | 13 ± 1 | 30 ± 3 | 25 ± 1†§ | 40 ± 2* |
| $\dot{V}O_2$max, ml min$^{-1}$ kg$^{-1}$ | 56 ± 2 | 43 ± 3 | 32 ± 2†§ | 24 ± 1† |

Values are means ± SE; *$P$ < 0.05, †$P$ < 0.01 post hoc significantly different from sex-matched young subjects.

### 2.5. Body composition and physical fitness

A dual-energy x-ray absorptiometry (DEXA) scanner (Hologic QDR Series Discovery A, Bedford, MA) was used to determine body fat, bone mineral tissue and residual tissue in each subject. Exercise testing was undertaken on a treadmill ergometer (H/P/Cosmos, Pulsar 4.0, Nussdorf-Traunstein, Germany), with initial workload set at 4 km/h at 5% gradient and step-wise increments in speed and grade every 3 min until volitional exhaustion. Heart rate and rhythm were continuously recorded by 12-lead ECG and all tests performed in older subjects were medically supervised. Oxygen consumption during exercise was directly calculated from minute ventilation, measured using a pneumotach and simultaneous breath-by-breath analysis of expired gas fractions (Medgraphics CPX/D and Ultima CardiO$_2$ systems, Minnesota). Maximal oxygen consumption was calculated as the highest consecutive 10 s period of gas exchange data occurring in the last minute before volitional exhaustion.

### 2.6. Exercise training program

Exercise training initially involved 3 sessions of exercise p/w at an intensity of 30% heart rate reserve (HRR) performed for 30 min per visit (treadmill walking and cycling). This regimen has been demonstrated to improve fitness and physiological function [14,15]. HRR was calculated using the following formula: ((Max HR − Resting HR) × intensity) + Resting HR. The resting and maximal heart rate measures were derived from the initial and repeat maximal exercise test. A Polar heart rate monitor (Polar Electro Oy, Kempele, Finland) was used to continuously monitor heart rate. Two sessions were supervised in a dedicated training facility, with the other session performed at home or in regional gymnasia. Compliance with the home-based component was assessed by regional site visits and regular telephone check-ups. After 6 weeks, the frequency increased to 5 sessions p/w. Repeat assessments were performed following 12 weeks of this regimen, after which the exercise intensity increased to 60% HRR. Further assessments were undertaken at 24 weeks. Four subjects (2 men, 2 women) acted as time controls, undergoing repeat testing at baseline and after 24 weeks.

### 2.7. Statistics

Statistical analyses were performed using Excel (Microsoft Office Excel 2007) and SPSS (SPSS, Chicago, Illinois). For the cross-sectional study, analysis of variance (ANOVA) and post hoc unpaired *t*-tests were used to assess significance of difference between groups. Repeated measures ANOVA and post hoc paired *t*-tests were used to examine the results for the intervention study. All data are reported as mean (SE) and statistical significance was assumed at $P < 0.05$.

**Table 2**
Subject characteristics of older sedentary men ($n = 6$) and women ($n = 5$) who underwent 24 wk of exercise (longitudinal study).

| | 0 wk | | 12 wk | | | | 24 wk | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Men | Women | Men | *P*-value | Women | *P*-value | Men | *P*-value | Women | *P*-value |
| Age, yr | 58 ± 2 | 62 ± 2 | 58 ± 2 | | 62 ± 2 | | 58 ± 2 | | 62 ± 2 | |
| SBP, mmHg | 125 ± 7 | 128 ± 7 | 120 ± 7 | <0.001 | 119 ± 6 | 0.12 | 120 ± 7 | 0.24 | 120 ± 6 | 0.35 |
| DBP, mmHg | 72 ± 3 | 72 ± 3 | 69 ± 3 | 0.25 | 66 ± 2 | 0.14 | 68 ± 4 | 0.34 | 64 ± 5 | 0.17 |
| BMI, kg/m$^2$ | 29 ± 2 | 29 ± 2 | 29 ± 2 | 0.75 | 28 ± 1 | 0.15 | 28 ± 2 | 0.43 | 27 ± 1 | 0.20 |
| % Body fat (DEXA) | 26 ± 1 | 38 ± 3 | 25 ± 1 | 0.18 | 38 ± 2 | 0.67 | 25 ± 1 | 0.15 | 36 ± 2 | 0.25 |
| $\dot{V}O_2$max, ml min$^{-1}$ kg$^{-1}$ | 30 ± 2 | 23 ± 2 | 33 ± 2 | 0.02 | 27 ± 2 | 0.05 | 39 ± 3 | <0.001 | 30 ± 2 | 0.003 |

Values are means ± SE. *P*-value represents the post hoc comparison between 12 or 24 wk and 0 wk.

## 3. Results

In total, 1183 of the 1296 individual training sessions were attended (91%; 87% in men and 95% in women) and subjects were closely monitored such that they maintained their prescribed HR during the supervised sessions.

### 3.1. Brachial versus popliteal artery

Wall thickness was higher in the popliteal artery than the brachial artery for both subject groups ($P < 0.01$, Fig. 1). Similarly, arterial diameter was higher for all within subject comparisons in the popliteal than the brachial artery ($P < 0.05$). Wall:lumen ratio data revealed differences between arteries in the Y and OS groups ($P < 0.05$).

### 3.2. Impact of age on brachial and popliteal artery characteristic

Comparison of the Y and OS groups revealed no significant impact upon wall thickness values with age (Fig. 1), whereas diameter values revealed a pattern of increase with age. Popliteal artery diameter was significantly higher in the OS than Y subjects ($P < 0.05$)

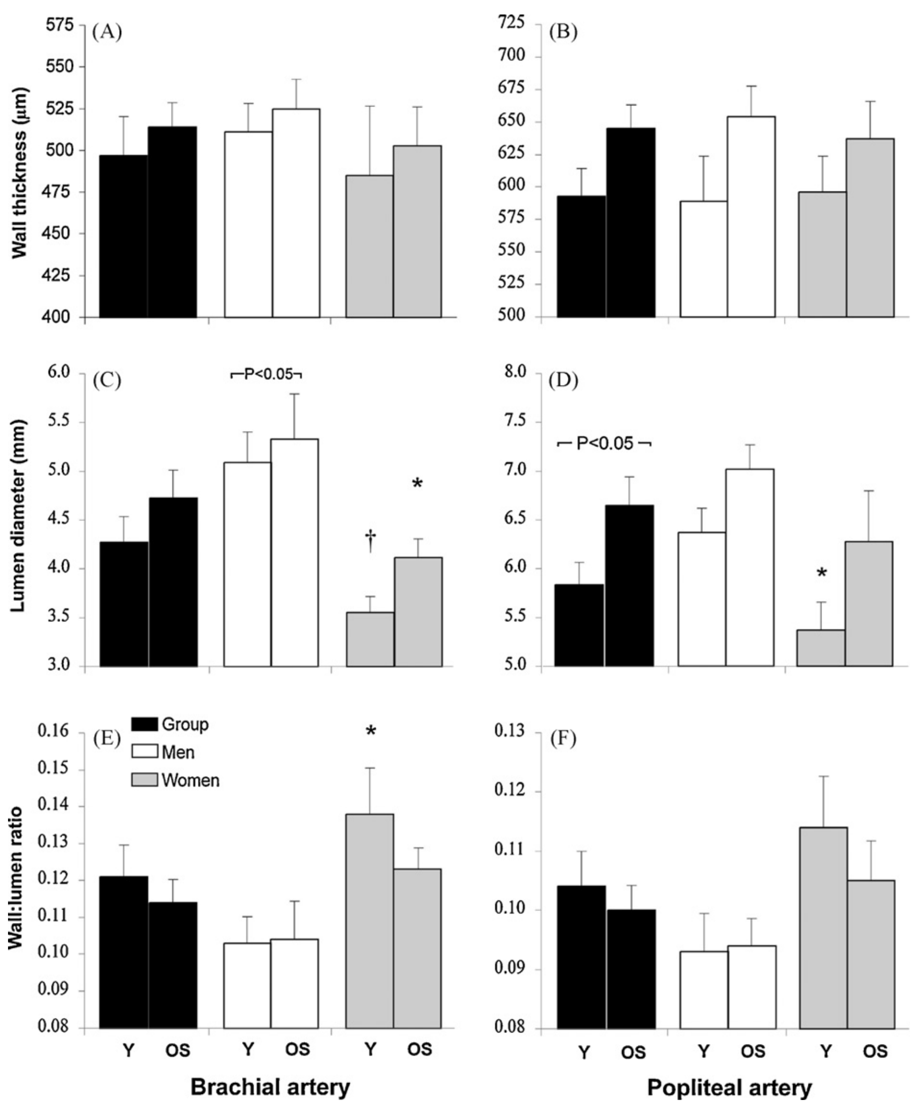


**Fig. 1.** Brachial and popliteal artery wall thickness (A, B), lumen diameter (C, D) and wall:lumen ratio (E, F) in young (Y: $n = 15$) and older sedentary (OS: $n = 16$) subjects. Data are presented for group (black bars), men (white bars), women (grey bars). Significant between men and women at *$P < 0.05$, †$P < 0.01$.

and OS men possessed significantly higher brachial artery diameters than their younger counterparts ($P<0.05$, Fig. 1). Consequently, a decrease in wall:lumen ratio was evident with age between the Y and OS groups, particularly for women, but this did not achieve statistical significance.

### 3.3. Impact of sex on brachial and popliteal artery characteristics

Whilst there were no significant differences in wall thickness between men and women for either artery, diameter was larger in both Y and OS men than in the corresponding groups of women in the brachial artery ($P<0.05$, Fig. 1). This was also true for the younger subjects in the popliteal artery ($P<0.05$).

When all men and women were compared, brachial wall:lumen ratio was significantly lower in men than women ($0.103 \pm 0.005$ versus $0.131 \pm 0.006$, $P<0.01$), due primarily to lower values in younger men versus younger women ($P<0.05$). Similarly, pooled male and female popliteal wall:lumen ratio data were lower in men ($0.094 \pm 0.004$ versus $0.109 \pm 0.005$, $P<0.05$, Fig. 1).

### 3.4. Impact of exercise training on brachial and popliteal artery characteristics

The longitudinal group data revealed significant decreases in both brachial and popliteal artery wall thickness between entry data and measures collected at both 12 and 24 weeks ($P<0.01$, Figs. 2 and 3). This trend was evident for both men and women, with differences observed in the brachial and popliteal arteries between entry and 24 weeks ($P<0.05$).

There was a general trend for increased lumen diameter in both men and women across the 24 week training period, and this achieved statistical significance in women, who demonstrated a significant increase in popliteal artery diameter between entry and week 24 ($P<0.05$).

The wall:lumen ratio data decreased with training. Group differences were evident between entry and 24 weeks in both the brachial ($P<0.01$) and popliteal arteries ($P<0.05$), with women demonstrating a significant decreases in wall:lumen ratio at 24 weeks in both arteries ($P<0.05$) and men demonstrating decreases at 12 weeks in the popliteal and 24 weeks ($P<0.05$) in the brachial artery.

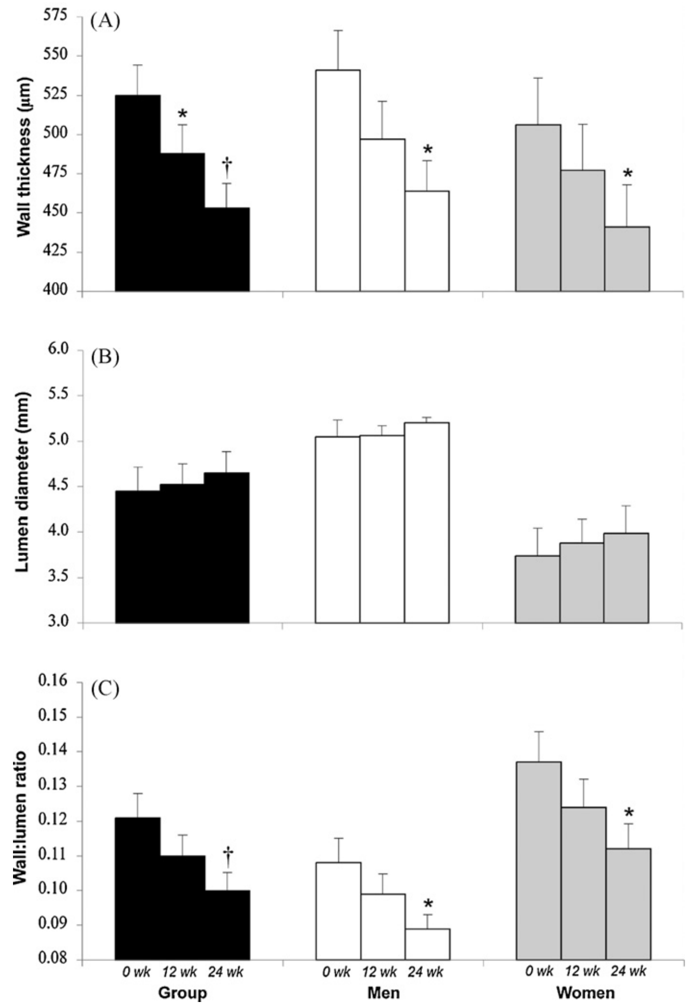


**Fig. 2.** Brachial artery wall thickness (A), lumen diameter (B), wall:lumen ratio (C) at baseline, 12 and 24 wk exercise training ($n=11$). Data is presented for the entire group ($n=11$, black bars), men ($n=6$, white bars) and women ($n=5$, grey bars). *Significant from week 0 at $P<0.05$, † $P<0.01$.

## 4. Discussion

We assessed artery wall thickness, lumen diameter and wall:lumen ratios in the popliteal and brachial arteries of healthy young and older sedentary individuals who subsequently undertook an exercise training program. This experimental design allowed us to examine the hypotheses that wall:lumen ratio would change to a greater extent with age in the popliteal than the brachial artery and that exercise training in sedentary older individuals would decrease arterial wall thickness and wall:lumen ratio in both upper and lower limb arteries.

Our first hypothesis relating age-related change to differential effects in the popliteal and brachial artery was based on the assumption that atherosclerosis preferentially affects arteries of the lower limb [17–20]. Symptomatic and gross morphological evidence of upper limb atherosclerosis is rare [16], whereas peripheral vascular disease is commonly associated with popliteal artery atherosclerosis. We therefore hypothesised that, if age is associated with atherosclerosis-related wall thickening, even in apparently healthy asymptomatic subjects, then we might observe differences between popliteal and brachial artery wall thickness between the young and older sedentary subjects. This is the first data, to our knowledge, to utilise comparisons between atherosclerosis-prone and -resistant arteries within individuals in order address the question of physiological versus pathological change. Our cross-sectional data indicate that, although there was a trend for increase in the wall thickness of OS compared to Y subjects, this was apparent in both the brachial and popliteal arteries. The lack of difference in age-related wall thickening between these arteries may relate to the relatively young age of our older subjects (~60 yrs), although it should be noted that previous studies of both femoral [5] and carotid [1] artery wall thickness reported large and significant differences between young, middle-aged and older men and women. It would be interesting to compare upper and lower limb wall thickness in an older cohort.

The fact that we observed trends for increase in wall thickness in both the brachial and popliteal arteries suggests that this may be a phenomenon that occurs in multiple vascular beds associated with ageing. Some previous studies have used changes in wall thickness (e.g. intima-medial thickness) of the carotid or peripheral conduit arteries as indices of atheromatous change [1,11]. Our result suggest that underlying changes associated with healthy ageing need to be considered when interpreting wall thickness as a marker of sub-clinical atheromatous change in future studies. As our findings indicate that the effects of exercise training occur systemically, rather than in a single artery or vascular bed, future studies should also assess the impact of interventions in more than one conduit artery.

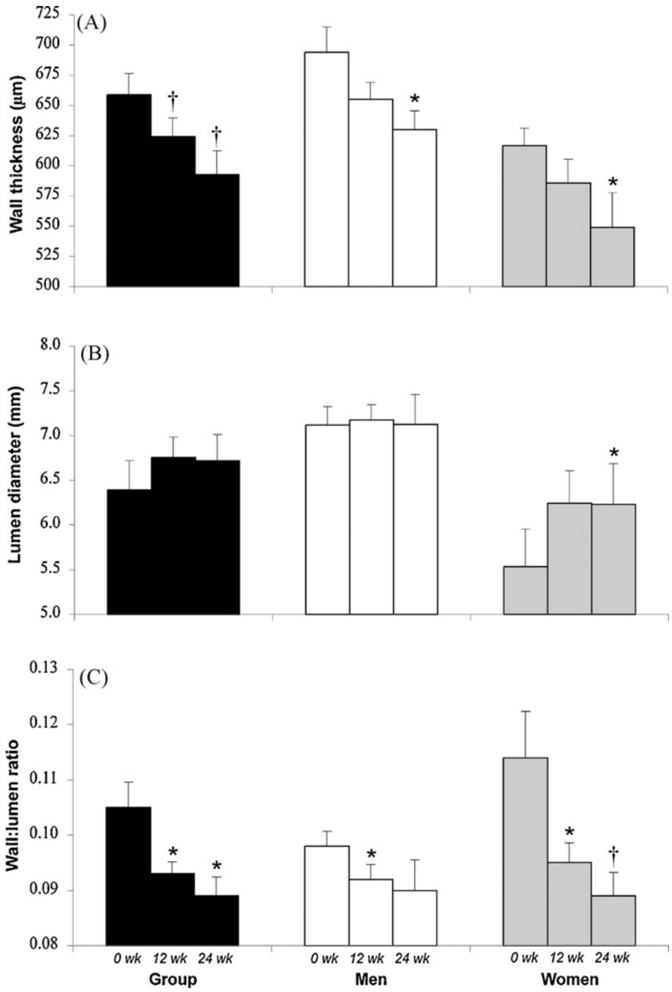


**Fig. 3.** Popliteal artery wall thickness (A), lumen diameter (B), wall:lumen ratio (C) at baseline (black bars), 12 wk (white bars) and 24 wk (grey bars) exercise training ($n = 11$). Significant from week 0 at $^*P < 0.05$, $^\dagger P < 0.01$.

Our findings suggest that wall:lumen ratio data may be higher in women than men, irrespective of subject age or the artery studied. This finding relates primarily to differences in lumen diameter between the sexes, as wall thickness values did not significantly differ between men and women. The implications of this sex difference are not clear, but Folkow et al. related increased wall:lumen ratio in resistance arteries to the aetiology of primary hypertension and increased vascular reactivity [17,18]. Further studies in larger samples of men and women will be required to fully address the question of whether the sex differences we observed in artery wall:lumen ratios between men and women are of clinical relevance.

The discussion above relates primarily to findings derived from cross-sectional experiments of young and older subjects. Such comparisons are limited by the variability associated with between-group analysis; that is, subjects may differ in many ways which can potentially influence artery wall thickness and remodelling, other than their age. To overcome such limitations, longitudinal designed experiments in which subjects act as their own controls are preferred. In the present study, we observed significant decreases in both wall thickness and wall:lumen ratio in older sedentary subjects exposed to an exercise regime. Changes were evident in both the brachial and popliteal arteries, suggesting that the impact of exercise on arterial remodelling *in vivo* is present across multiple vascular bed. Previous longitudinal evidence pertaining to the impact of exercise training on arterial wall thickness and remodelling is scant and typically examined a single artery only. In two studies from one laboratory, Dinenno et al. observed decreases in femoral artery wall thickness and wall:lumen ratio following 3-months exercise training in middle-aged and older subjects [11], whereas Tanaka et al. found no changes in carotid artery following a similar protocol [1]. The ~90 µm decrease in femoral artery wall thickness observed by Dinenno et al. [11] is comparable to the ~70 µm decrease we observed in the popliteal and brachial artery. Rakobowchuk et al. also observed no change in carotid wall thickness in young healthy subjects following either low volume sprint interval training or high volume endurance training [19]. Other studies, performed in overweight and obese children, observed decreases in carotid artery wall thickness following 6 [20] and 12-months [21] of exercise training. Finally, we recently observed decreases in brachial artery wall thickness and wall:lumen ratio following 3 months of resistance, but not aerobic, exercise training, in patients with advanced heart failure. Taken together, these studies suggest that exercise training can modify wall thickness, particularly in older individuals or those with cardiovascular risk factors. Our findings in the current experiment add the important observation that such effects are present in upper and lower limbs and evident in conduit arteries feeding both active and inactive skeletal muscle vascular muscle beds.

The present study benefited from a combination of both cross-sectional and longitudinal experimental designs, adopted operator-independent and validated edge-detection and wall-tracking software and assessed changes in response to individually prescribed and closely supervised exercise training. However, there are also some limitations to this experiment. Our sample size, whilst consistent with that used in previous similar experiments, was nonetheless relatively modest. However, due to the large effect sizes and reproducibility of our technique, the (sub)group analyses were adequately powered to demonstrate significant effects of age, gender and fitness. In addition, we did not specifically recruit and randomise older sedentary subjects to an inactive control group. We did, however, collect repeat data at 24 weeks on 4 older sedentary subjects who did not undertake exercise training. In contrast to the trained group, data from these subjects revealed an *increase* in wall thickness (brachial: $496 \pm 18$ to $502 \pm 23$ µm; popliteal: $644 \pm 43$ to $751 \pm 23$ µm) and in the wall:lumen ratio (brachial: $0.091 \pm 0.009$ to $0.104 \pm 0.010$; popliteal: $0.086 \pm 0.008$ to $0.112 \pm 0.006$). A previous study found a ~300 µm larger femoral artery wall thickness in older subjects compared with their younger counterparts [22]. Based on this marked effect of ageing, the increase in wall thickness in older subjects across 24 weeks is not inconsistent with the literature. Nonetheless, this "control" data should be considered cautiously, given the small number of subjects involved. Our data therefore suggests that exercise training reverses the underlying trend associated with the passage of time alone.

In summary, our cross-sectional comparison of young and healthy, but sedentary, older subjects indicated that, whilst there was a consistent trend for increase in the wall thickness for both the brachial and popliteal arteries, there was limited evidence to support our hypothesis that wall:lumen ratio changed to a greater extent with age in the popliteal than the brachial artery. Our data also suggest that the relative increase in arterial lumen diameter with age exceeds that in wall thickness and that this change is not limited to a single vascular bed, as it was apparent in both upper and lower limb conduit arteries. Our longitudinal training data revealed decreases within subjects in wall thickness and wall:lumen ratio in both arteries. These findings suggest that exercise training is associated with beneficial effects on conduit artery wall thickness and wall:lumen ratio in the upper and lower limbs in humans.

## Disclosure statement

None of the authors have conflict to disclosure.


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