Real-World Training for a First-Time Marathon Reverses Age-Related Aortic Stiffening: A Prospective Longitudinal Cohort Study.

Brief title: Vascular ageing and first-time marathon training.

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Abstract

Background Ageing increases aortic stiffness, contributing to cardiovascular risk even in healthy individuals. Aortic stiffness is reduced through supervised training programmes, but these are not easily generalizable.

Objective To determine whether real-world exercise training for a first-time marathon can reverse age-related aortic stiffening.

Methods Untrained healthy individuals underwent six-months of training for the London Marathon. Assessment pre-training and two weeks post-marathon included central (aortic) blood pressure (cBP), and aortic stiffness using cardiovascular magnetic resonance distensibility. Biological 'aortic age' was calculated from the baseline chronological age-stiffness relationship. Change in stiffness was assessed at the ascending (Ao-A) and descending aorta at the pulmonary artery bifurcation (Ao-P) and diaphragm (Ao-D). Data are mean changes (95% confidence intervals).

Results 138 first-time marathon completers (age 21-69 years, 49% male) were assessed, with an estimated training schedule of 6-13 miles per week. At baseline, a decade of chronological ageing correlated with a decrease in Ao-A, Ao-P and Ao-D distensibility by 2.3, 1.9, and $3.1x10^{-3}.mmHg^{-1}$ respectively ($p<0.05$ for all).

Training decreased systolic and diastolic cBP by 4(2.8,5.5) and 3(1.6,3.5)mmHg. Descending aortic distensibility increased (Ao-P:9%,p=0.009; Ao-D:16%,p=0.002), whilst remaining unchanged in the Ao-A. These translated to a reduction in 'aortic age' by 3.9(1.1,7.6) and 4.0(1.7,8.0)years (Ao-P and Ao-D respectively). Benefit was greater in older, male participants with slower running times ($p<0.05$ for all).

Conclusions Training for and completing a marathon even at relatively low exercise intensity reduces central blood pressure and aortic stiffness- equivalent to a ~4-year reduction in vascular age. Greater rejuvenation was observed in older, slower individuals.

Condensed Abstract

A hallmark of normal ageing is arterial stiffening, which increases the cardiovascular risk even in healthy individuals. Because supervised training programmes are not easily generalizable, we investigated the effects of real-world exercise on vascular ageing in a prospective longitudinal cohort. 138 untrained individuals underwent assessment pre-training and two weeks after a first marathon of aortic stiffness by cardiovascular magnetic resonance and central (aortic) blood pressure. Exercise training reduced aortic stiffness, equivalent to a four-year reduction in vascular age, and blood pressure, comparable to anti-hypertensive medication. These benefits were greater in older, male, slower runners despite relatively low exercise intensity.

Keywords: Marathon; exercise training; aortic stiffness; blood pressure; ageing; cardiovascular magnetic resonance.

Abbreviations

ß-stiffness	Beta-stiffness (pressure-independent stiffness)
CMR	Cardiovascular Magnetic Resonance
CPET	Cardio-Pulmonary Exercise Test
DBP	Diastolic Blood Pressure
Peak VO_2	Maximal oxygen consumption
PP	Pulse Pressure
PWV	Pulse wave velocity
SBP	Systolic Blood Pressure

Introduction

Ageing is a major risk factor for cardiovascular disease beyond simple cumulative conventional risk factor exposure. In large arteries, advancing age is associated with biochemical and histological changes that result in vessel stiffening. The aorta buffers pulsatile stroke volume and translates this to steady peripheral flow, therefore progressive stiffening increases pulse pressure (PP) and ventricular afterload. Such changes in hemodynamics are associated with dementia, cardiovascular and kidney disease,(1–3) even in the absence of atherosclerosis,(4) suggesting that age-related arterial stiffening is detrimental to health. Anti-hypertensive agents can modify arterial stiffness once established in disease, but more cardiovascular events occur in individuals without diagnosed hypertension,(5) providing an opportunity for early lifestyle modification in health.(6,7)

One potential beneficial strategy is regular aerobic exercise.(8) Mass participation running is an increasingly popular form of non-prescribed exercise, with 18 million finishers in the USA in 2018.(9) Cross-sectional studies have shown that lifelong athletes possess more distensible peripheral arteries,(10) and relatively brief (< 3 months) supervised aerobic exercise interventions benefit brachial blood pressure (BP) and peripheral artery stiffness.(11,12) The dose of exercise needed to preserve or even rejuvenate the central (aortic) arterial system in a real-world setting is not known. Using cardiovascular magnetic resonance, it is now possible to assess local arterial stiffness by distensibility in the aorta rather than peripheral vessels. This is a stronger prognostic marker, and is more closely associated with the natural ageing process.(13–15) Because the aorta has varying tissue composition, local distensibility measured at discrete levels may facilitate the detection of regional influences.

We hypothesized that age-related aortic stiffening in health would be reversible with real-world exercise training. To explore this, we used a large cohort of healthy, first-time

marathon runners investigated before training initiation, and after completion of the London Marathon.

Methods

Study population and assessment timing

Healthy participants were recruited into a prospective longitudinal observational study to investigate the effect of first-time marathon training on cardiovascular function. Participants were recruited over the 2016 and 2017 London Marathons (Virgin Money). Details of the study have been reported previously.(16) Inclusion criteria were: no significant past medical history; no previous marathon-running experience (approximately half of ~50,000 receiving ballot places each year); and current participation in running for <2 hours per week. In 2016, participants of age 18-35 years were included and in 2017, adults of all ages were included. Exclusion criteria were: pre-existing cardiovascular disease during preliminary investigations, or contraindication to CMR. All procedures were in accordance with the principles of the Helsinki declaration, all participants gave written informed consent and the study was approved by the London-Queen Square National Research Ethics Service Committee (15/LO/0086).

All measurements were conducted before training started, immediately after the release of the results from the ballot entry system six months prior to the marathon. These were repeated within 3 weeks after completion of the London Marathon, but not earlier than one week after completion to avoid the acute effects of exercise. In this analysis, participants were included if they had successfully completed the marathon and attended both baseline and follow-up assessments. 237 participants were recruited, 71 did not run the Marathon (52 due to injury), and 139 completers attended follow-up. One participant started anti-hypertensive medication after the baseline assessment and was excluded from subsequent

analysis. Participants who dropped out had similar baseline anthropomorphic, blood pressure and arterial stiffness measurements, Online Table 1.

Exercise training

Participants were recommended to follow the "Beginner's Training Plan" provided by the marathon organizers with the aim of achieving marathon completion rather than improvement in cardiovascular fitness. This consists of approximately 3 runs per week, increasing in difficulty for a 17-week period leading into the London Marathon race (https://bit.ly/1UOPwiN).(17) Those who wished to follow alternative, higher intensity or longer training plans were however not discouraged from doing so.

Data acquisition and analysis

Peripheral BP, central BP, anthropomorphic, and cardio-pulmonary exercise test assessments are described in the Online Methods. After BP acquisition, CMR was performed at 1.5T (Magnetom Aera, Siemens AG Healthcare, Erlangen, Germany). Single-shot ECG-gated white blood sagittal aortic ('candy cane') views were acquired first to measure 3D aortic length and to standardize cross-sectional imaging. This was used to pilot axial aortic blood flow-velocity maps at the level of the pulmonary artery bifurcation and the level of the diaphragmatic descending thoracic aorta. The spoiled gradient echo phase-contrast sequence used was free-breathing, ECG-gated and segmented, with the following parameters: acquired temporal resolution 9.2ms (reconstructed to 100 cardiac phases per RR interval); spatial resolution 1.97 x 1.77 mm^2; slice thickness 6mm; through-plane velocity encoding 150cm/s; field of view 192 x 108mm; flip angle 20˚. The contours for the ascending, proximal and distal (diaphragmatic) descending aorta were traced semi-automatically using validated software (ArtFun) on the phase-contrast modulus for area analysis, and velocity images to derive velocity profiles.(18) Analysis was performed with the operator blinded to the scan timing (baseline or follow up), and with the paired scans analysed independently. Using

ascending aortic pressure and flow-velocity waveforms, wave separation analysis was used to compute the ascending aortic wave speed, characteristic impedance and reflection magnitude, taken as the ratio of the backward to the forward wave amplitudes.(19)

Local, regional and whole aortic stiffness

Because the aorta is known to have varying regional tissue composition, local arterial stiffness was measured by distensibility at three levels of the thoracic aorta. Arterial stiffness may mechanistically reflect either intrinsic changes in the arterial wall or the functional effect of loading conditions, therefore, beta (ß)-stiffness index was also calculated. This is a pressure-independent measure of intrinsic arterial stiffness because it accounts for the non-linear compliance to pressure relationship.

$$Distensibility = \frac{A_{max} - A_{min}}{A_{min} \times cPP \times 1000}\ 10^{-3}.mmHg^{-1}$$

where A_{max} and A_{min} are the maximum and minimum aortic areas across the cardiac cycle.

$$\beta = \frac{\ln(cSBP/cDBP)}{(d_s/d_d) - 1} - \ln(\frac{cDBP}{P_{ref}})$$

where d_s and d_d are the maximum and minimum aortic diameters calculated from the areas and P_{ref} is a reference BP, here 100mmHg. Because a single central PP estimate was used for distensibility calculation at each level of the aorta, a sensitivity analysis was undertaken to model the likely impact of neglect of PP amplification on the estimates of distensibility using the changes in PP from ascending to the diaphragmatic descending aorta reported in a previous study.(20) This suggested neglect of PP amplification would only have small effects and would be unlikely to substantively alter the findings of the study.

Pulse wave velocity (PWV) was measured from the transit time between velocity profiles to derive average aortic stiffness across the length of the whole aorta, and regional ascending, and descending thoracic aortic segments. Further details, and reproducibility of all measures, are available in the Online Methods.

Biological aortic age

Biological aortic age was determined from the relationship between age and local aortic stiffness at each level of the aorta using the baseline cross-sectional data, Online Methods. Aortic stiffness is strongly correlated with chronological age, and so any deviations from expected values may reflect between-subject susceptibility to accelerated ageing, or conversely, vascular adaptation.

Statistical analysis

Data were analysed in R (R foundation, Vienna, Austria) using RStudio Server version 1.0.153 (Boston, Mass, USA). All continuous variables are expressed as mean±SD or median (interquartile range [IQR]) for skewed data, and the 95 percent confidence interval of the changes with exercise training. Baseline and follow-up data were compared using paired Student's t-tests for normally distributed continuous variables or Mann-Whitney U test and the Chi-square tests for non-normally distributed and categorical variables respectively. Because the study was designed to look at older and younger participants, age groups were a priori stratified by the mean age of the cohort (37 years), similar to Tanaka et al.(14) To minimize the influence of outliers, extreme data points (greater than six interquartile ranges below the first or above the third quartile) were removed (8 out of 1668 data points in aortic stiffness measures pre- and post- training).

Linear regression was used to assess independent relationships after adjusting for covariates, and partial correlation coefficients ($r_{partial}$) were used to describe the associations. Associations between aortic stiffness and baseline BP, heart rate, weight, body fat, marathon completion time and peak VO_2 were adjusted for age and sex. Associations between aortic stiffness and sex were adjusted for age and peak VO_2. Because aortic stiffness is partly dependent on loading conditions, the association between the change in aortic distensibility and change in systolic blood pressure (SBP) was adjusted for the 'operating' BP (baseline

mean central arterial pressure). Changes between aortic stiffness and other dependent variables at follow-up were adjusted for the baseline measurement of the covariate. To determine whether the change in aortic stiffness was attributable to a change in intrinsic structure, the change in distensibility was adjusted for the change in operating BP, and the change in β-stiffness was examined. Linear regression model diagnostics were inspected, and data were power transformed if appropriate to satisfy the assumptions of constant variance and normality of residuals. All tests were two-tailed and a p value of <0.05 was considered statistically significant. For primary end-points, a 0.10 false discovery rate, according to the method described by Benjamini and Hochberg, was used to determine significant associations.

Results

Participants

138 first-time marathon completers attended assessment 176±11 days before and 16±4 days after marathon completion. The mean age was 37±10 years (range: 21-69 years) and 49% were male. Participant characteristics at baseline and follow-up are summarized in Table 1. Average marathon running time was 5.4±1.0 hours for women and 4.5±0.8 hours for men, Figure 1. Based on weekly training data and marathon completion times from 27,000 runners, these timings are consistent with a training schedule of between 6 and 13 miles per week.(21)

Baseline ageing and aortic stiffness

For the ascending, proximal descending and diaphragmatic descending aorta, a decade of ageing resulted in a decrease in distensibility by 2.3, 1.9, and 3.1 $x10.^{-3}mmHg^{-1}$ and an increase in ß-stiffness by 27, 22, and 16% respectively, Online Figure 2.

Effect of training on blood pressure and heart rate

Brachial SBP and DBP decreased with training by 4 (2.8, 5.5) and 3 (1.6,3.5) mmHg respectively,$p<0.01$ for both. Central SBP and DBP decreased with training by 4 (2.5,5.3) and 3 (1.6,3.5) mmHg respectively, $p<0.001$ for both, Figure 2. There was no significant change in heart rate with training (-2.3 [0.3,-4.3]beats per minute), p=0.07.

Effect of training on regional aortic stiffness

Aortic stiffness reduced with training, and was more pronounced in the distal aorta, Table 2. Distensibility did not change in the ascending aorta (p=0.14), but increased by 9% and 16% in the proximal descending and diaphragmatic descending aorta, p=0.009 and 0.002 respectively, Online Table 2. The change in distensibility was independent of the change in mean arterial pressure ($p<0.001$ for the descending aorta). β-stiffness showed less pronounced but similar regional trends. β-stiffness did not change in the ascending (p=0.60) or proximal descending aorta (p=0.08), but decreased by 6% in the diaphragmatic descending aorta (p=0.04), Figure 3. The change in β-stiffness was not associated with the change in distensibility in the ascending (p=0.13) or proximal descending aorta (p=0.11), but explained 42% of the change in distensibility in the diaphragmatic descending aorta ($p<0.001$). PWV showed similar but less pronounced regional trends to local distensibility measurements, Table 2.

Effect of training on biological aortic age

After training, the increase in distensibility translated to a reduction in biological aortic age by 1.5 (-0.9,5.4; p=0.16), 3.9 (1.1, 7.6; p=0.009) and 4.0 (1.7,8.0;

p=0.002) years in the ascending, proximal descending and diaphragmatic descending aorta respectively. When estimated from β-stiffness, biological aortic age reduced by 0 (-2.8,2.8; p=0.99), 2.4 (-0.5,5.3; p=0.11) and 3.2 (0.1,6.2; p=0.04) years in the ascending, proximal descending and diaphragmatic descending aorta respectively, Online Table 2.

Associations with the training-related change in aortic stiffness

Increasing age was associated with greater reduction in either measure of aortic stiffness in the descending aorta (greatest $r_{partial}$ 0.21, p=0.02), Table 2 and Figure 2. Males had a greater reduction than females in descending aorta β-stiffness ($r_{partial}$ 0.19 and 0.16, p=0.03 and p=0.03 respectively) when adjusted for age and peak VO_2. This was equivalent to a median 1.4 year greater benefit in men. Higher baseline central SBP was associated with a greater reduction in β-stiffness of the proximal and diaphragmatic descending aorta ($r_{partial}$ 0.23 and 0.21, p=0.006 and 0.02 respectively). The strength of these associations were reduced when adjusted for age and sex ($r_{partial}$ 0.16 and 0.20, p=0.06 and 0.02 respectively). There was no association between baseline central SBP and the change in distensibility with training. With training, a greater reduction in either measure of aortic stiffness was associated with a greater reduction in SBP, adjusted for loading conditions (greatest $r_{partial}$ -0.31, p<0.001), Online Table 3.

Slower marathon running time was associated with a greater increase in proximal descending aortic distensibility with exercise training ($r_{partial}$ -0.20, p=0.02), Online Table 3. There was no association with the change in β-stiffness and marathon performance. Baseline peak VO_2, heart rate, body fat, and weight or alterations in these parameters with training were not associated with the change in either measure of aortic stiffness with training.

Discussion

This prospective longitudinal cohort study shows that six-months of training and completion of a first-time marathon is sufficient to achieve reductions in blood pressure and aortic stiffness. It was possible to reverse the consequences of ageing on vessel stiffening by approximately four years, as measured in the aorta rather than more peripheral vessels. Both brachial and aortic SBP reduced by 4 mmHg, a magnitude comparable to first line anti-hypertensive medications.(22) Benefits were observed in healthy individuals across a broad age range, and were greater in older, slower, male marathon runners with higher baseline BP. Performance times were suggestive of achievable exercise doses in real-world novice participants– approximately thirty minutes slower than the average completion time for the London Marathon. Based on completion times, participants trained for 6-13 miles a week, in line with the suggested 17-week training program and within the recommendations of the 2018 USA Physical Activity Guidelines.(23)

In healthy individuals, chronological ageing leads to a gradual increase in aortic stiffness and elevated cardiovascular risk. However, chronological age is not the same as the biological process which captures life course influences, and frames how we make choices that can accelerate or rejuvenate the vasculature.(24) Cross-sectional studies have shown that moderate intensity exercise at 4-5 days a week preserves ‘youthful’ compliance of the carotid artery.(25) However it is important to know both the effect of exercise on aortic rather than peripheral arterial stiffening given its greater prognostic importance, and the mechanism of changes in stiffness.(6) Cross-sectional findings may be attributable to genetic or confounding influences, and vascular capacitance itself may determine exercise capacity. Several studies have demonstrated the efficacy of supervised training programmes that prescribe the type, dose and frequency of exercise.(12,26) Examining the consequences of first-time marathon training helps to understand the benefits from real-world exercise

behavior that people enjoy and may continue if motivated and free from injury. A goal-orientated exercise training recommendation ("*sign-up for a marathon*" or "*run a fun-run*") can be a good motivator to keep active and may increase the likelihood of sustaining benefits. This study emphasizes the importance of lifestyle to modify the ageing process, particularly as it appears "never too late" to gain the benefit as seen in older, slower runners.(27)

In this context, this study contributes a number of findings in a large real-world cohort comprising both sexes. The relative reduction in SBP observed is comparable to antihypertensive medication, given the participants in this study were normotensive and a greater improvement was observed in those with higher SBP.(28) Persistent reductions in SBP of this magnitude reduce stroke mortality by over 10% and avoid large numbers of premature deaths in the general population.(29) Both reductions in aortic stiffness and BP are in keeping with the magnitude of benefit from other aerobic exercise interventions.(30) There was a small change in peak VO_2 which did not explain the change in stiffness, contrary to expectation, but also observed in other studies.(11,31) The training program was designed to habituate individuals to sustained running rather than augment fitness,(17) and this is supported by a previous study in this cohort showing greater improvements in skeletal muscle peak VO_2 than cardio-pulmonary peak VO_2.(16) Changes in stiffness were also not associated with changes in other measures (heart rate, weight or adiposity), suggesting that the hemodynamic impact of more frequent exercise sessions and lifestyle modification has a direct effect on intrinsic aortic remodeling.

The improvement in aortic stiffness was both functional due to blood pressure lowering, as well as intrinsic due to structural changes in the descending aorta, Figure 4. This is supported by wave separation analysis which showed reflection magnitude was unchanged. One study of 13 males observed similar benefits after just four weeks of training,(32) but other studies of two to four months duration observed that the reduction in stiffness was

predominantly functional.(33,34) Unlike previous studies, we used direct CMR assessment of the aorta and over a longer duration of training for aortic remodeling. Differences in intrinsic stiffness may be due to endothelial function, smooth muscle tone or dietary factors but were beyond the measurement scope of this study.(31) Older, male runners had a greater reduction in aortic stiffness, attributable to greater baseline BP and aortic stiffness. Whilst aortic stiffening increases significantly after the age of 50, these data suggest that this is in part modifiable in non-hypertensive individuals.(35) Slower marathon runners also had a greater reduction in distensibility from higher baseline measures of stiffness, although directionality can only be assumed in this study.

Structural properties may explain the preferential effect of exercise on the descending thoracic aorta. The proximal aorta media has a higher elastin:collagen ratio to maintain high compliance.(36) Conversely, the distal aorta media contains a higher proportion of smooth muscle that may be more readily modifiable within a six-month period.(15) The effect of both exercise and combination medication have previously been noted to have an effect on the arterial tree that can vary by 25% depending on the branch.(34,37) Regional (PWV) and local (distensibility) measurement of aortic stiffness both capture this heterogeneity, but are associated with different cardiovascular outcomes, and demonstrate distinct sensitivities to downstream pathological manifestations of arterial stiffening.(14,38) Local measurement may be more sensitive to regional changes associated with exercise training because it can resolve subtle changes that can summatively contribute to whole vessel hemodynamics.

Study limitations

This study was conducted in healthy individuals, therefore our findings may not apply to patients with hypertension who have stiffer arteries that may be less modifiable.(39) From these data, however, those with higher SBP at baseline appeared to derive greater benefit. This study was not designed to provide structured training, but rather to observe the

effects of real-world preparation for a marathon which randomized control trials cannot address. Nevertheless, information on the intensity, frequency and type of exercise training would have been valuable to understand further the beneficial effects on aortic stiffness. The modest change in peak VO_2 may be related to exercise training intensity or low adherence, which reflects the real-world. Peak VO_2 was performed semi-supine to allow concurrent echocardiography and this may also have reduced sensitivity to changes due to running, or running efficiency. We assessed only marathon finishers – plausibly, non-finishers could have had different vascular responsiveness. The causal link of exercise to measured changes is only inferred - marathon training may lead to other lifestyle modifications (dietary, other behavioral factors), or alterations in lipid profiles and glucose metabolism – although these have not been previously associated with changes in aortic stiffness.(11) We did not examine the effect of exercise on peripheral arteries or endothelial dysfunction. Whilst individual participants served as internal controls, there may have been run-in bias for the initial blood pressure measurement. This appears unlikely as blood pressure changes would not have been age-related nor correlated with the change in separate measures (eg. aortic stiffness) with training. Estimated aortic ages are approximations and based on the same dataset at baseline rather than independent observations. The exercise dose-response curve here is not sampled – only training for a first-time marathon with single timepoint assessment. This area warrants further study. We measured distensibility on modulus imaging acquired at 1.5T rather than steady-state free precession imaging. The free-breathing sequence we used achieved good temporal resolution but may be susceptible to through-plane motion. However, this and similar sequences correlate well with breath-held cine imaging, and show similar associations with ageing.(18) If error were introduced into distensibility measurements related to through-plane motion, the resultant noise would minimise the effect size related to exercise training, and therefore would be unlikely to account for our key findings. PP undergoes amplification

from central to more peripheral locations, typically being ~6mmHg higher in the descending thoracic than the ascending aorta.(20) This PP amplification is not accounted for in our analysis since it would have involved invasive measures of aortic pressure at each locations. A sensitivity analysis suggested that the likely impact of this effect on the observed changes after training would be minimal; however, we cannot completely exclude the possibility that changes in PP amplification contribute to the observed differences. Diaphragmatic descending aortic distensibility data reported here were however higher than expected, although there is limited literature for comparison.(40) Unlike Voges et al, central rather than brachial PP was used which would explain greater distensibility, and the use of 1.5T phase-contrast modulus may accentuate image contrast differences between 3T gradient echo sequences.(40)

Conclusion

Training and completion of a first-time marathon result in beneficial reductions in blood pressure and intrinsic aortic stiffening in healthy participants. These changes are equivalent to approximately a four-year reduction in vascular age. Greater benefit was observed in older, slower, male marathon runners with higher baseline blood pressure.

Clinical Perspectives

Core Clinical Competencies: Increased aortic stiffness and central aortic blood pressure, both strong predictors of cardiovascular mortality, are lowered in healthy individuals after six-months training for and completion of a first-time marathon. The benefit was greater in older, slower, male individuals. Lifestyle advice to partake in unsupervised, popular forms of exercise training that people enjoy and are likely to continue may be an effective strategy to reduce the effects of age-related arterial stiffening.

Translational Outlook: The vascular benefits of exercise are observed at relatively low exercise doses in real-world training programmes. The exercise dose-response curve is not yet completely known, and so the optimum real-world exercise training schedule for maximum benefit requires further study. Training had some direct impact on intrinsic aortic remodeling, but the mechanism of these changes is not yet known.

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Figure legends

Figure 1 London Marathon running times for study participants. Vertical lines represent the average of the median running times for the 2016 and 2017 London Marathons.

Figure 2 Greater change with exercise training in aortic blood pressure (top) and distensibility (bottom) in older age category (>37 years old). Data are medians and standard errors. *Abbreviations: * p<0.05; ** p<0.01;*** p<0.001; **** p<0.0001*.

Figure 3 Baseline central (aortic) systolic blood pressure, aortic stiffness and estimated aortic age; and the change (red arrow) with exercise training for the average older marathon completer.

Figure 4 Reduction in aortic stiffness with exercise stiffness is due to both intrinsic structural (load-independent) and functional (pressure-dependent) changes. At higher arterial pressure, the aorta is functionally stiffer, but this relationship is not linear. Exercise training results in a reduction in pressure-dependent distensibility (leftward shift along the curve), and additionally a reduction in intrinsic β-stiffness (upward shift of the curve), contributing to a greater reduction in stiffness (red arrows and lines). In this schematic, data are fitted to an exponential for the cohort both before and after exercise training.

Central Illustration Training and completion of a first-time marathon reverses age-related aortic stiffening and reduces central (aortic) blood pressure. Biological aortic age was calculated from the baseline age-stiffness relationship at assessment six months before and two weeks after a first marathon. The reduction in aortic stiffness was equivalent to a four-year reduction in estimated aortic age. These benefits were greater in older, male, slower runners with higher baseline systolic blood pressure (BP), in adjusted models. Data are the linear age-stiffness relationship before and after exercise training (left); systolic, diastolic BP and mean arterial pressure (top right); and marathon running times (bottom right). Abbreviations: *= p<0.05.

	Whole cohort			Older (>37 years)			Younger (≤37 years)		
	Baseline	**Follow-up**	***p***	**Baseline**	**Follow-up**	***p***	**Baseline**	**Follow-up**	***p***
n	138			59			79		
Age (years)	37 (21-69)			47 ±7			30 ±4		
Male	68 (49%)			28 (47%)			40 (51%)		
Running Time (hrs)	4.96 ±0.98			5.37 ±1.05			4.65 ±0.80		
Weight (kg)	73 ±13	72 ±12	*0.002*	75 ±14	73 ±13	*<0.001*	72 ±13	71 ±12	*0.59*
Body Fat (%)	25 ±8	24 ±9	*0.009*	28 ±7	26 ±8	*0.01*	23 ±8	23 ±9	*0.34*
Peak V02 (ml/kg/min)	34.5 ±7.5	35.6 ±8.3	*0.02*	31 ±6.5	32.0 ±6.7	*0.048*	37 ±7.0	39 ±8.3	*0.06*
Heart Rate (bpm)	69 (61,77)	67 (61,75)	*0.07*	69 (61,78)	67 (58,77)	*0.29*	69 (61,76)	67 (62,75)	*0.14*
Blood Pressure (mmHg)									
Brachial SBP	120 (111,128)	116 (108,124)	*<0.001*	124 (114,132)	120 (109,127)	*<0.001*	118 (110,124)	114 (108,122)	*0.004*
Brachial DBP	75 (70,79)	72 (68,76)	*<0.001*	78 (74,82)	74 (67,77)	*<0.001*	73 (70,77)	71 (68,76)	*0.016*
Brachial MAP	90 (85,95)	88 (81,92)	*<0.001*	94 (87,98)	89 (82,93)	*<0.001*	88 (83,92)	86 (81,90)	*0.005*
Brachial PP	45 (40,51)	44 (40,50)	*0.004*	46 (42,54)	44 (40,52)	*0.03*	45 (40,49)	43 (40,47)	*0.053*
Central SBP	110 (102,121)	106 (100,114)	*<0.001*	116 (109,123)	109 (101,119)	*<0.001*	108 (100,114)	104 (100,111)	*0.002*
Central DBP	76 (72,81)	74 (69,78)	*<0.001*	79 (75,83)	75 (69,79)	*<0.001*	74 (71,78)	73 (69,77)	*0.02*
Central MAP	87 (82,94)	85 (79,90)	*<0.001*	92 (87,96)	86 (80,92)	*<0.001*	85 (82,90)	83 (79,88)	*0.007*
Central PP	35 (31,41)	33 (30,39)	*0.02*	39 (33,43)	35 (32,41)	*0.056*	33 (29,39)	33 (30,37)	*0.19*
Wave separation (mmHg)									
Forward pressure wave	98 (92,105)	95 (88,101)	*<0.001*	102 (96,107)	96 (90,104)	*0.002*	95 (90,103)	93 (88,100)	*0.01*
Backward pressure wave	13 (12,16)	12 (11,15)	*0.009*	14 (12,16)	14 (11,16)	*0.16*	12 (10,14)	11.31 (10,13)	*0.06*
Reflection magnitude	0.55 (0.50,0.62)	0.54 (0.51,0.6)	*0.60*	0.57 (0.51,0.64)	0.55 (0.52,0.61)	*0.66*	0.54 (0.49,0.61)	0.54 (0.49,0.59)	*0.70*

Table 1 Baseline characteristics and follow-up response to exercise, stratified by older (>37 years) and younger (≤37 years) participants. Data are mean (±standard deviation; full age range for whole cohort) or median (inter-quartile range). 1 participant did not have follow-up cardiovascular magnetic resonance due to pregnancy; 3 participants had partial aortic phase contrast acquisition due to scanner crashes; 1 participant imaging data was not saved successfully at one time-point. 5 participants did not have cardiopulmonary exercise testing data due to either machine crashes or injury at follow-up. Wave separation waves are measured in the ascending aorta. *Abbreviations: SBP= systolic blood pressure, DBP= diastolic blood pressure; MAP= mean arterial pressure; PP= pulse pressure.*

	Whole cohort			Older (>37 years)			Younger (≤37 years)		
	Baseline	**Follow up**	***p***	**Baseline**	**Follow up**	***p***	**Baseline**	**Follow up**	***p***
n	138			59			79		
Distensibility ($x10^{-3}.mmHg^{-1}$)									
Ascending	8.6 (5,11)	8.5 (6,12)	-	5.4 (3,8)	5.9 (4,9)	*0.04*	10.3 (8,13)	10.6 (8,13)	-
Proximal Descending	8.6 (6,12)	9.1 (6,13)	*0.009*	6.2 (4,10)	7.1 (5,10)	*0.02*	9.2 (8,14)	10.8 (8,14)	-
Diaphragmatic Descending	13.7 (11,18)	15.2 (12,21)	*0.002*	11.7 (9,14)	12.7 (10,17)	*<0.001*	16.0 (13,20)	16.6 (14,23)	-
Beta-stiffness									
Ascending	2.9 (2.5,4.2)	3.1 (2.4,4.2)	-	4.2 (3.3,6.8)	4.1 (3.1,6.0)	-	2.7 (2.1,2.9)	2.6 (2.2,3.3)	-
Proximal Descending	3.1 (2.4,4.3)	2.9 (2.3,4.0)	*0.08*	3.9 (2.7,5.6)	3.9 (2.7,4.9)	-	2.7 (2.2,3.4)	2.6 (2.1,3.2)	-
Diaphragmatic Descending	2.0 (1.7,2.3)	1.9 (1.6,2.3)	*0.04*	2.3 (2.0,2.7)	2.1 (1.9,2.5)	*0.051*	1.8 (1.6,2.1)	1.8 (1.5,2.2)	-
Vascular age (Distensibility)									
Ascending	39.3 (28,53)	39.9 (24,52)	-	53.1 (43,63)	51.2 (37,59)	*0.04*	32.0 (20,40)	31.0 (19,44)	-
Proximal Descending	40.0 (22,55)	37.5 (19,51)	*0.009*	53.4 (34,63)	48.0 (35,59)	*0.02*	28.1 (10,44)	28.6 (12,42)	-
Diaphragmatic Descending	41.4 (28,51)	36.4 (19,48)	*0.002*	47.8 (41,57)	44.6 (32,53)	*<0.001*	33.6 (20,44)	31.8 (12,41)	-
Vascular age (Beta-stiffness)									
Ascending	38.3 ±17.9	38.6 ±16.8	-	50.1 ±17.7	48.5 ±17.2	-	29.4 11.9	30.9 ±11.6	-
Proximal Descending	37.1 ±20.5	34.8 ±19.0	*0.11*	46.3 ±22.0	43.2 ±20.4	-	30.3 16.4	28.4 ±15.2	-
Diaphragmatic Descending	37.2 ±17.5	33.6 ±18.6	*0.04*	46.1 ±17.4	40.4 ±20.0	*0.051*	30.4 14.4	28.4 ±15.5	-
Pulse wave velocity (m/s)									
Arch	4.4 (4,5)	4.2 (4,5)	-	5.4 (5,6)	5.3 (4,6)	*0.09*	3.9 (3,4)	3.9 (4,4)	-
Descending Aorta	7.9 (6,10)	7.4 (6,9)	*0.06*	8.1 (7,10)	7.7 (7,10)	-	7.6 (6,10)	7.1 (6,9)	*0.08*
Whole Aorta	5.7 (5,7)	5.5 (5,6)	*0.03*	6.3 (6,7)	6.1 (5,8)	-	5.1 (5,6)	5.0 (5,6)	*0.10*
Ascending aortic Z_c (dynes.s.cm^{-5})	59 ±18	57 ±14	-	60 ±20	57 ±15	-	57 ±15	56 ±12	-
Ascending aortic wave speed (m/s)	3.3 (3,4)	3.0 (3,4)	-	3.7 (3,4)	3.7 (3,4)	-	3.0 (2,4)	2.8 (2,3)	*0.08*
Diameter (mm)									

Ascending	28 ±4	28 ±4	-	30 ±4	30 ±4	-	26 ±3	26 ±3	-
Proximal Descending	21 ±3	20 ±3	*0.10*	21 ±3	21 ±3	-	20 ±3	19 ±3	*0.04*
Diaphragmatic descending	17 ±2	17 ±3	-	18 ±2	18 ±3	-	16 ±2	16 ±2	-

Table 2 Aortic stiffness before and after exercise training, stratified by older (>37 years) and younger (≤37 years) participants. Data are mean (±standard deviation) or median (inter-quartile range). Only p values which are significant at 0.10 false discovery rate are reported.
Abbreviations: Z_c=Characteristic impedance.