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Curriculum in Pathophysiology and Disease Prevention

EFFECTS OF MEDIUM-TERM, UNSUPERVISED, MILD INTENSITY PHYSICAL TRAINING ON CARDIOVASCULAR REMODELLING AND KNEE JOINT DAMAGE IN YOUNG AND MIDDLE-AGED HEALTHY SEDENTARY INDIVIDUALS.

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EFFETTI DELL'ALLENAMENTO FISICO NON SUPERVISIONATO DI LIEVE INTENSITA' E MEDIA DURATA SUL RIMODELLAMENTO CARDIOVASCOLARE E SULLA PATOLOGIA DELL'ARTICOLAZIONE DEL GINOCCHIO IN INDIVIDUI SEDENTARI DI GIOVANE E MEZZA ETA'.

Introduzione. Col progredire dell'età, la capacità dell'organismo di modificare struttura e funzione di organi e apparati in risposta agli stimoli si modifica. Scopo di questo progetto è indagare l'effetto dell'età sul rimodellamento cardiovascolare in risposta all'allenamento aerobico e valutare gli effetti della corsa sulla patologia del ginocchio.

Metodi. 237 volontari sani, sedentari, sono stati valutati al basale e dopo 6 mesi di allenamento non supervisionato e il completamento della loro prima maratona, con: 1) risonanza magnetica cardiaca a 1.5T; 2) misurazione non invasiva della pressione arteriosa (PA) centrale e brachiale; 3) risonanza magnetica (MRI) bilaterale del ginocchio a 3.0T. La "età aortica biologica" è stata calcolata al basale dalla relazione tra l'età anagrafica e la rigidità arteriosa. Modificazioni nella rigidità arteriosa sono state valutate a livello dell'aorta ascendente (Ao-A), discendente (Ao-D), della biforcazione polmonare (Ao-P) e del passaggio diaframmatico (Ao-D).Per l'analisi, i soggetti sono stati divisi in due gruppi in base all'età (≥35 anni: O35; ≤34 anni: U35).

Risultati. Le percentuali di infortunio e completamento della corsa sono state simili nei due gruppi. 138 corridori (U35: n =71, femmine =49%; O35: n =67, femmine =51%) hanno completato la corsa. In media, gli U35 sono stati 37 minuti più veloci (12%). L'allenamento si è associato a un piccolo incremento nella massa del ventricolo sinistro (LV) in entrambi i gruppi ($3 g/m^2$, $p < 0.001$), ma negli U35 si è osservato anche un aumento del volume biventricolare (volume telediastolico LV [EDV]i +3%; volume telesistolico LV [ESV]i +8%; EDVi del ventricolo destro [RV] +4%, RVESVi +5%; $p<0.01$ per tutti).

La compliance sistemica aortica si è ridotta nell'intero campione del 7% ($p=0.020$) e, in particolare negli O35, anche le resistenze vascolari sistemiche (-4% nell'intero campione, $p=0.04$) e la PA (sistolica/diastolica, intero campione: brachiale -4/-3 mmHg, centrale -4/-2 mmHg, tutti $p <0.001$; O35: brachiale -6/-3 mmHg, centrale -6/-4 mmHg, tutti $p<0.001$). Al basale, una decade di età anagrafica corrispondeva a una riduzione della distensibilità Ao-A, Ao-P, e Ao-D di 2.3, 1.9, and 3.1 x 10^{-3} mm Hg^{-1} rispettivamente ($p < 0.05$ per tutti). La distensibilità di Ao-D è aumentata (Ao-P: 9%; $p = 0.009$; Ao-D: 16%; $p = 0.002$), mentre quella di Ao-A è rimasta invariata. Queste variazioni corrispondono a una riduzione nella "età aortica" di 3.9 anni (95% CI: da 1.1 a 7.6 anni) e 4.0 anni (95% CI: da 1.7 a 8.0 years) (Ao-P e Ao-D, rispettivamente). Il beneficio è stato maggiore in partecipanti di sesso maschile, più anziani e più lenti ($p < 0.05$ per tutti).

La MRI basale ha mostrato segni di danno asintomatico in numerose strutture del ginocchio nella maggioranza degli 82 soggetti esaminati. Dopo la maratona, la MRI ha mostrato una riduzione del punteggio di danno nell'edema midollare subcondrale nei condili tibiali ($p=0.011$) e femorali ($p=0.082$).

Conclusioni. In soggetti sani e sedentari, un allenamento fisico non supervisionato, di intensità lieve e di media durata induce variazioni misurabili nella struttura e funzione cardiovascolare. L'entità di queste variazioni è dipendente dall'età, con maggior rimodellamento cardiaco osservato nei più giovani e maggior rimodellamento vascolare osservato nei più anziani, fino a una riduzione della PA centrale e rigidità arteriosa equivalenti a una riduzione di ~ 4 anni nell'età vascolare. Inoltre, l'allenamento e corsa di una maratona non sono lesivi sull'articolazione del ginocchio.

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Background. Healthy ageing is associated with changes in human's body ability to modify organs and systems structure and function in response to stimuli. With this project we sought to understand whether remodelling in response to a stimulus, exercise training, altered with healthy ageing and to deepen the knowledge about running effects on the knee joint.

Methods. 237 untrained healthy male and female subjects volunteering for their first-time marathon were recruited. At baseline and after 6 months of unsupervised training, race completers underwent tests including 1.5T cardiac magnetic resonance, brachial and non-invasive central blood pressure (BP) assessment and a 3.0T bilateral knee magnetic resonance. 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). For analysis, runners were divided by age (O35: ≥35y.o.; U35: ≤ 34y.o.)

Results. Injury and completion rates were similar among groups. 138 runners (under 35 [U35]: n=71, females=49%; over 35 [O35]: n=67, females=51%) completed the race. On average, U35 were faster by 37 minutes (12%). Training induced a small increase in left ventricle (LV) mass in both groups (3g/m^2, p<0.001), but U35 also increased ventricular cavity sizes (LV end-diastolic volume [EDV]i +3%; LV end-systolic volume [ESV]i +8%; right ventricle [RV] EDVi +4%, RVESVi +5%; p<0.01 for all).

Systemic aortic compliance fell in the whole sample by 7% (p=0.020) and, especially in O35, also systemic vascular resistance (-4% in the whole sample, p=0.04) and blood pressure (systolic/diastolic, whole sample: brachial -4/-3 mmHg, central -4/-2 mmHg, all p <0.001; O35: brachial -6/-3 mmHg, central -6/-4 mmHg, all p<0.001). 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 3.1 x 10^{-3} mm Hg^{-1}, respectively (p < 0.05 for all). Descending aortic distensibility increased (Ao-P: 9%; p = 0.009; Ao-D: 16%; p = 0.002), while remaining unchanged in the Ao-A. These translated to a reduction in "aortic age" by 3.9 years (95% CI: 1.1 to 7.6 years) and 4.0 years (95% CI: 1.7 to 8.0 years) (Ao-P and Ao-D, respectively). The benefit was greater in older, male participants with slower running times (p < 0.05 for all).

Pre marathon and pretraining MRI showed signs of damage, without symptoms, to several knee structures in the majority of the 82 middle-aged volunteers. However, after the marathon, MRI showed a reduction in the radiological score of damage in subchondral bone marrow oedema in the condyles of the tibia (p=0.011) and femur (p=0.082).

Conclusion. Medium-term, unsupervised, mild intensity physical training in healthy sedentary individuals induces measurable remodelling of both heart and vasculature. This amount is age-dependent, with predominant cardiac remodelling when younger and predominant vascular when older, with a reduction in central blood pressure and aortic stiffness equivalent to a ~ 4-year reduction in vascular age. Training for and running a marathon is associated with improvement in the condition of bone marrow and articular cartilage.

Table of Contents

List of abbreviations

ACLOAS	Anterior cruciate ligament osteoarthritis
BLOKS	Boston-Leeds osteoarthritis knee score
BME	Bone marrow oedema
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CI	Confidence interval
CMR	Cardiac magnetic resonance
CO	Cardiac output
CPET	Cardio-pulmonary exercise test
DBP	Diastolic blood pressure
ECG	Electrocardiogram
ECV	Extracellular volume
EDTA	ethylenediaminetatraacetic acid
EDV	End-diastolic volume
ESV	End systolic volume
FDR	False discovery rate
HFpEF	Heart failure with preserved ejection fraction
HR	Heart rate
ITBFS	iliotibial band friction syndrome
KOOS	Knee injury and osteoarthritis outcome score
KOSS	Knee osteoarthritis scoring system
LAV	Left atrium volume
LGE	Late gadolinium enhancement
LQTS	Long QT syndrome
LV	Left ventricle
MAP	Mean arterial pressure
MCID	Minimal clinically important difference
MOAKS	Mri osteoarthritis knee score
MOLLI	Modified look-locker inversion
MRI	Magnetic resonance imaging
O35	Over 35
OUES	oxygen uptake efficiency slope
PD FS	proton density-weighted fat suppressed
PP	Pulsatory pressure
PWV	Pulse wave velocity
RQ	Respiratory quotient
RV	Right ventricle
SAC	Systemic arterial compliance
SBP	Systolic blood pressure

SD	Standard deviation
SVR	Systemic Vascular resistance
TE	Echo time
TEM	Technical error of measurement
TR	Repetition time
U35	Under 35
WORMS	Whole-organ magnetic resonance imaging score

Introduction

The human body can dynamically modify the structure and function of many organs and systems in response to stimuli, either intrinsic or extrinsic. This ability, defined “plasticity”, can be observed macroscopically during pregnancy, but also in the brain, where neural networks change through growth and reorganization, in the musculoskeletal system, where muscles grow or shrink, acquire or lose endurance and flexibility in response to use and, of course, in the cardiovascular system. Plasticity, and thus the final phenotype, at a given time point is determined by multiple factors including age, sex, environmental factors, disease and genetics. [1]–[4]

Among the unmodifiable factors affecting body function, structure and plasticity, age must be mentioned. Generalizing, there is an inverse relationship between plasticity and age, where younger subjects show higher ability to enact structural and functional changes. Most age-related biologic functions peak before age 30 and gradually decline linearly thereafter. This is due to multiple factors which, in an extreme simplification, can be summarized with progressive cell loss and changes in extracellular matrix composition. [5] These modifications affect the function of all systems (e.g. blood pressure increase, loss of muscular mass, loss of bone mineralization, impaired senses, reduced brain performance, reduced ventilatory reserve, impaired kidney function etc).

On the other hand, physical exercise is probably the most important extrinsic factor able to induce favourable remodelling of tissues and systems. Aerobic physical exercise is widely prescribed as a key nonpharmacological mean to promote general and brain health, reducing cardiovascular risk, delaying the onset or slowing down the progression of chronic degenerative conditions, speeding up fitness restoration after acute events and heart surgery.[1], [6]–[8]

The effect of training on healthy ageing is of particular interest considering the progressive population ageing and the wide prescription of aerobic training in cardiovascular patients. In fact, people aged over 65 are expected to represent the 22% of the population by 2040, with a prevalence of cardiovascular disease in this age group > 40%, [9], [10] due both to reduced mortality from acute

events and to the emergence of new phenotypes of cardiac diseases, such as heart failure with preserved ejection fraction (HFpEF).

Cardiac Remodelling

"Cardiac plasticity" is the ability of the myocardium to undergo reversible structural and functional changes via "remodelling", a process that appears evolved to optimize performance in any given preload and overload conditions. [1] It starts at the molecular level and involves to a variable extent apoptosis and hypertrophy of myocytes, [2] hyperplasia of capillary endothelial cells and interstitial fibroblasts [11][3] and changes in the extracellular matrix. These modifications eventually translate into changes in wall thickness, chambers volume and global ventricular function, with a growth range of the myocardium that can exceed 100%. [1] The overall cardiovascular phenotype at any given time is determined by age, sex, [12] environmental factors (sedentary vs athletic), disease and genetics.[13][14], [15]

It is now accepted that the traditional "physiological" versus "pathological" remodelling dichotomic classification is an oversimplification of a multi-layered, context-sensitive and sophisticated continuum. Overlapping features might be observed in athlete's heart, early dilated or hypertrophic cardiomyopathy and left ventricular non-compaction. At the same time, the healthy ageing heart shares diastolic function impairment with heart failure with HFpEF. [13]

Multiple coexisting factors contribute to remodelling: 1) intrinsic factors, such as gender and genetic substrate; 2) the ageing process; 3) external stimuli. [14],[12]

On the one hand, sex differences in cardiovascular structure and function, possibly related to hormonal status and fitness level, [16], [17] and the power of family history to identify a genetic predisposition to disease, has been appreciated for some time. [18]

On the other hand, a slow but progressive loss of cardiomyocytes appears as a function of age, in humans and in animals. [2], [3] An autoptic study demonstrated that the average number of myocytes drops from $6.0x10^9 \pm 1.8x10^9$ at 17-30 years to $4.0x10^9 + 1.3x10^9$ at 65-90 years, i.e. by 33%. [3] This

loss in muscle mass is accompanied by a progressive increase in myocyte cell volume tending to compensate for the loss of functioning muscle and resulting in preservation of ventricular wall thickness. However, the cellular hypertrophic response is unable to maintain normal cardiac mass, which decreases proportionally to age. [3] At the same time, a modification in the contractile proteins, in the myocardial Ca2+ channels and in the cardiac collagen (both a focal increase and a change in its physical properties, due to nonenzymatic cross-linking) also occur within the ageing myocardium. [19], [20]

Finally, external stimuli, including modification in volume and pressure load and neurohumoral activation, can trigger remodelling. [21] This kind of plasticity, observed for example during pregnancy, physical training or prolonged bed rest, is dose-dependent and can be reversible. At an adequate dose, external stimuli can be major determinants of the final cardiac phenotype, and recent evidence point out that long-term physical exercise from early middle age can even slow down age-related increase in cardiac stiffening. [23]

In athletes, the final cardiac phenotype is determined by both the amount and kind of exercise. In the mid-1970s, Morganroth and colleagues [22] proposed a dichotomous characterisation of the athlete's heart. Specifically, the increased volume load observed during endurance training would lead to eccentric heart remodelling (i.e. increase in ventricular volumes, modest wall thickening, a low relative wall thickness) associated with reductions in resting heart rate, whilst the increased pressure load observed in strength and power-based sports would lead to concentric remodelling (i.e. thick ventricular walls, relatively small ventricular volumes, and a high relative wall thickness) with minimal change in heart rate.

Until recently, this view has been widely accepted in the sports cardiology literature. However, whilst this hypothesis is attractive from a physiological basis, it is likely an over-simplistic representation of cardiac remodelling in response to athletic training and does not take into account that most sport disciplines move onto a continuum between pressure and volume load.

Vascular Remodelling

The vascular wall is a multi-layered structure composed by endothelium, smooth muscle cells, and fibroblasts interacting to form an autocrine-paracrine complex. Vascularization is a dynamic process in which the final vascular structure and function are partly guided by changes in the environment. After growth, vessels still remain receptive to external stimuli and thus able to undergo remodelling in response to long-standing changes in hemodynamic conditions. Vascular remodelling is an active process of structural change that involves changes in at least four cellular processes: cell growth, cell death, cell migration, and the synthesis or degradation of extracellular matrix; however, it may subsequently contribute to the pathophysiology of vascular diseases and circulatory disorders. [24]

As Epstein and colleagues [24] nicely illustrate, vascular remodelling shows different characteristics when developed following main changes in pressure load, volume load or a direct injury. Similarly to what observed in the heart, an increase in arterial pressure leads to wall thickening and relative lumen reduction. The wall thickening can be either determined by an increase in muscle mass (

Figure 1, vessel A) or rearrangements of cellular and noncellular elements (

Figure 1, vessel B). These changes are associated with heightened vascular reactivity, which adds to the increase in peripheral resistance observed in hypertension. [8]

Another form of vascular remodelling is determined by changes in volume load and is characterized by an unchanged wall thickness with an increased lumen or harmonic reduction in both wall thickness and vascular lumen (

Figure 1, vessels C and D). Clinical examples of this form of remodelling include the vascular dilatation associated with sustained high blood flow (

Figure 1, vessel D) (e.g., an arteriovenous fistula) or the cell loss and matrix proteolysis that result in aneurysm formation. Indeed, rarefaction of the microcirculation (a loss of capillary area) is another form of vascular remodelling that promotes hypertension and tissue ischemia. [25] Finally, the architecture of the vessel wall is also markedly altered in response to vascular injury (

Figure 1, vessels E and F). A neointima forms as part of a reparative response to injury that involves thrombosis, migration and proliferation of vascular cells, matrix production, and inflammatory cell infiltration.

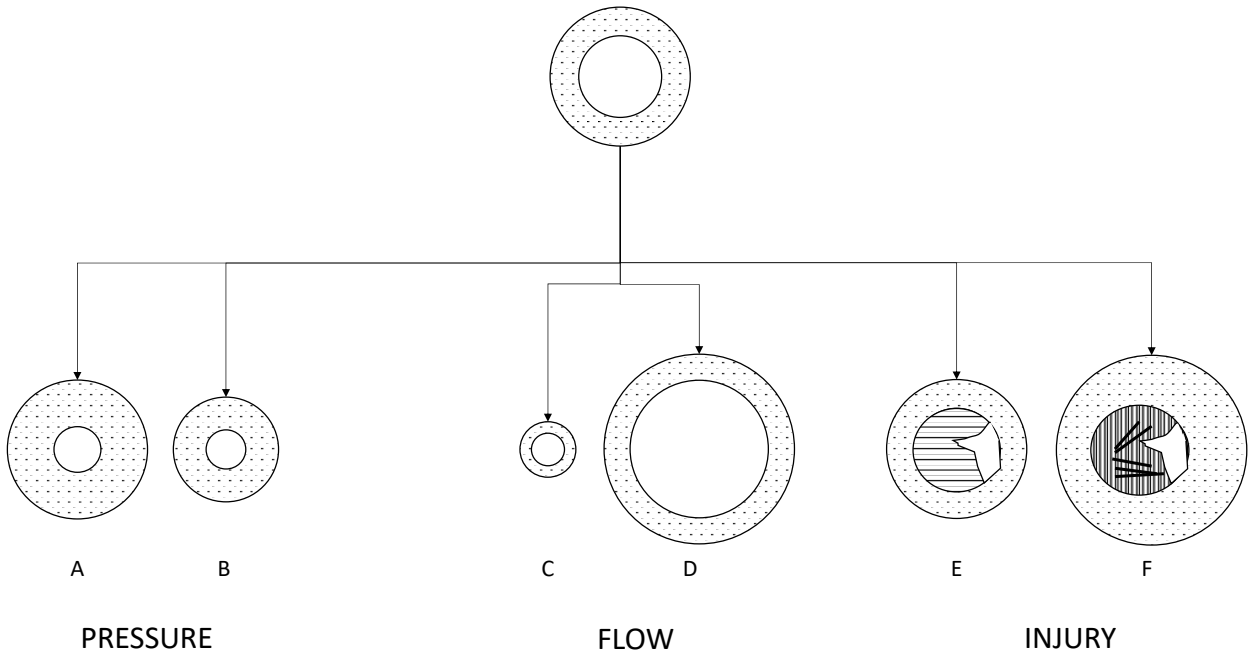

Figure 1: Adapted from Epstein et al [24] The Spectrum of Vascular Remodelling. Vessel A represents hypertensive vascular disease with vascular hypertrophy, in which the medial layer is thickened and the luminal diameter is reduced; vessel B, hypertensive vascular disease without medial hypertrophy, in which the luminal diameter is reduced; vessel C, decreased vessel dimensions in response to a long-term decrease in flow; vessel D, increased vessel dimensions in response to a long-term increase in flow; vessel E, neointimal hyperplasia (migration and proliferation of vascular smooth-muscle cells) in response to vascular injury; and vessel F, atherosclerosis in response to vascular injury of conduit vessels.

In large arteries, advancing age is associated with biochemical and histological changes that result in vessel stiffening, similar to what observed in hypertensive patients. 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 hemodynamic are associated with dementia and cardiovascular and kidney disease, [8], [26] even in the absence of atherosclerosis, [27] suggesting that age-related arterial stiffening is detrimental to health. Antihypertensive agents can

modify arterial stiffness once established in disease, but more cardiovascular events occur in individuals without diagnosed hypertension, [28] providing an opportunity for early lifestyle modification in health. [29], [30] One potential beneficial strategy is regular aerobic exercise. [31] Cross-sectional studies have shown that lifelong athletes possess more distensible peripheral arteries, [32] and relatively brief (<3 months) supervised aerobic exercise interventions benefit brachial blood pressure (BP) and peripheral artery stiffness.[33], [34] 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 (CMR), it is now possible to assess local arterial stiffness by distensibility in the aorta rather than peripheral vessels. [35] This is a stronger prognostic marker and is more closely associated with the natural ageing process. [36], [37] Because the aorta has varying tissue composition, local distensibility measured at discrete levels may facilitate the detection of regional influences.

Cardiac and vascular interaction

Cardiac and vascular function are closely related. In fact, the two compartments, i.e. heart and vasculature, interact directly via vascular coupling (volume and pressure loading) and through paracrine and neurohumoral control. [21], [38] This interplay between cardiac function and arterial system, which in turn affects ventricular performance, is a key determinant of global cardiovascular performance and an expression of global cardiovascular efficiency. This relation can be expressed in mathematical terms as the ratio between arterial elastance (EA) and end-systolic elastance (EES) of the left ventricle (LV). In practice, EES indicates how much the LV end-systolic volume increases and stroke volume decreases in response to an elevation of end-systolic pressure. The potentials of the application of ventricular-arterial coupling in clinical practice are large, in particular in the field of hypertension,[39] heart failure,[40], [41] coronary artery disease, [42]and valvular heart disease.[43]

Osteoarticular system

Running exerts repetitive stress on the lower extremities, especially the knee joint, therefore, in excess, can lead to injuries and the development of osteoarthritis. [44], [45] Nevertheless, the actual quantity and quality of exercise needed to induce knee damage are not known. So far, previous studies have only found few subtle short-term abnormalities, i.e. non-acute lesions, of low grade of severity on magnetic resonance imaging (MRI) scans of the knees of regular long-distance runners (minutes to few weeks after the marathon); this was where no significant pre-existing injuries were reported in the first place.[45]–[48] At the same time, preparation for a marathon has been linked to an incidence of musculoskeletal problems as high as 90%, especially at the knee joint including patellofemoral pain.[48]

Limited peer-reviewed data on the impact of marathon running over a longer period of time (medium-term, 2–3-month follow-up; long-term, one study 10-year follow-up) has shown that any immediate post-marathon alterations in MRI signal return to baseline in runners within 3 months.[48], [49] All follow-up studies up to this point were conducted with a very small population of regular long-distance runners (up to 13 participants; one knee scanned only),[48], [49] and none studied the incidence and status of running-related lesions over time in novice runners participating in their first marathon.

Pathologies of the knee joint increase with age and may be already existing before middle age, even without symptoms.[50] In fact, both well and poorly functioning knees can have similar damage, making it difficult to correlate relevant MRI findings with the patients' knee pain.[51], [52] Advice on permitted load and stress limits in asymptomatic knee pathologies to prevent from advancing osteoarthritis (OA) remain unclear. [50]

MRI has a high sensitivity for the detection of subtle changes of joint structures.[49] The estimated prevalence of MRI lesions in asymptomatic knees varies significantly between studies, from 0

to 75%.[51], [53] This is due to varying study designs, including different MRI field strengths and sequences employed - indicative of variation in diagnostic accuracy [54], [54] - as well as cohorts of varying size and levels of physical activity. [50]

Aim of the study

With this study, we wished to explore the relationship between healthy ageing and differences in cardiovascular adaptation in response to a stimulus, here mild, unsupervised, medium-term aerobic exercise. Furthermore, we wished to determine the prevalence of abnormal knee findings in asymptomatic adults, to better understand the effect of marathon running on the knee joint and to better understand the implications of long-distance running for the knees of novice runners.

Methods

Over two consecutive years, subjects were recruited from the London Virgin Money Marathon ballot winners into a prospective longitudinal observational study. Only runners recruited the second year were included in the orthopaedic study.

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).

Inclusion criteria

- Aged 18 years and over at recruitment
- First-time marathon runner
- Able to provide written informed consent

Exclusion criteria

- Hypertension
- Previous cardiac disease history
- Use of anabolic steroids and/or performance-enhancing drugs
- Cardiac disease uncovered during preliminary examination
- Absolute contraindications to cardiac MRI scanning
- Pregnant or breastfeeding women.
- Only for orthopaedic study: known knee damage and/or reported pain.
- Other conditions (e.g. history of neoplasia, mediastinal radiotherapy, autoimmune diseases etc) were evaluated case by case by the Investigators.

London Virgin Money Marathon

The London Virgin Money Marathon is a major event held in London yearly, which was very well-suited for our purpose. London Marathon runners require no prior experience and there is no qualifying time as a barrier to race entry, with the majority taking part as first-time marathon runners. Furthermore, the number of people willing to participate in this marathon is such that general public places are allocated through a ballot, with >75000 application/year against ~50000 available places. Ballot results are usually announced in October. The uncertainty about the ballot results discourages prospective first-time marathon runners from starting training too early and allowed us to recruit and assess our entire sample over 2 weeks, while still at their true "fitness baseline".

Recruitment process.

The study was advertised by email over two consecutive years to novice marathon runners, identified through the database records of the Virgin Money London Marathon, and on social media. Interested runners contacted a dedicated call centre and were given an appointment for eligibility assessment and recruitment.

Running training

Subjects were encouraged to follow a beginner's training plan, consisting of approximately three runs per week, increasing in difficulty over a 17-week period leading up to the London Marathon race, which is the recommendation of the race organizers (London Marathon, 2018) (Beginner 17 Weeks Training Plan in Supplementary Material). The proposed training was of increasing intensity over the weeks (it also included interval training sessions). Subjects wishing to follow alternative, higher intensity training plans were not discouraged from doing so. All runners were asked to submit weekly training updates, either by email or sharing the data of available commercial trackers (e.g. FitBit, Garmin watch…).

Study plan

All runners underwent all the study tests within 16 days from ballots results, approximately 6 months before the race. In each runner, all tests were performed on the same day, as described in Figure 2 (average tests duration: 6 hours). At follow-up, tests were performed with the same modality, 14 to 18 days after the marathon in order to avoid the acute effects of the race.

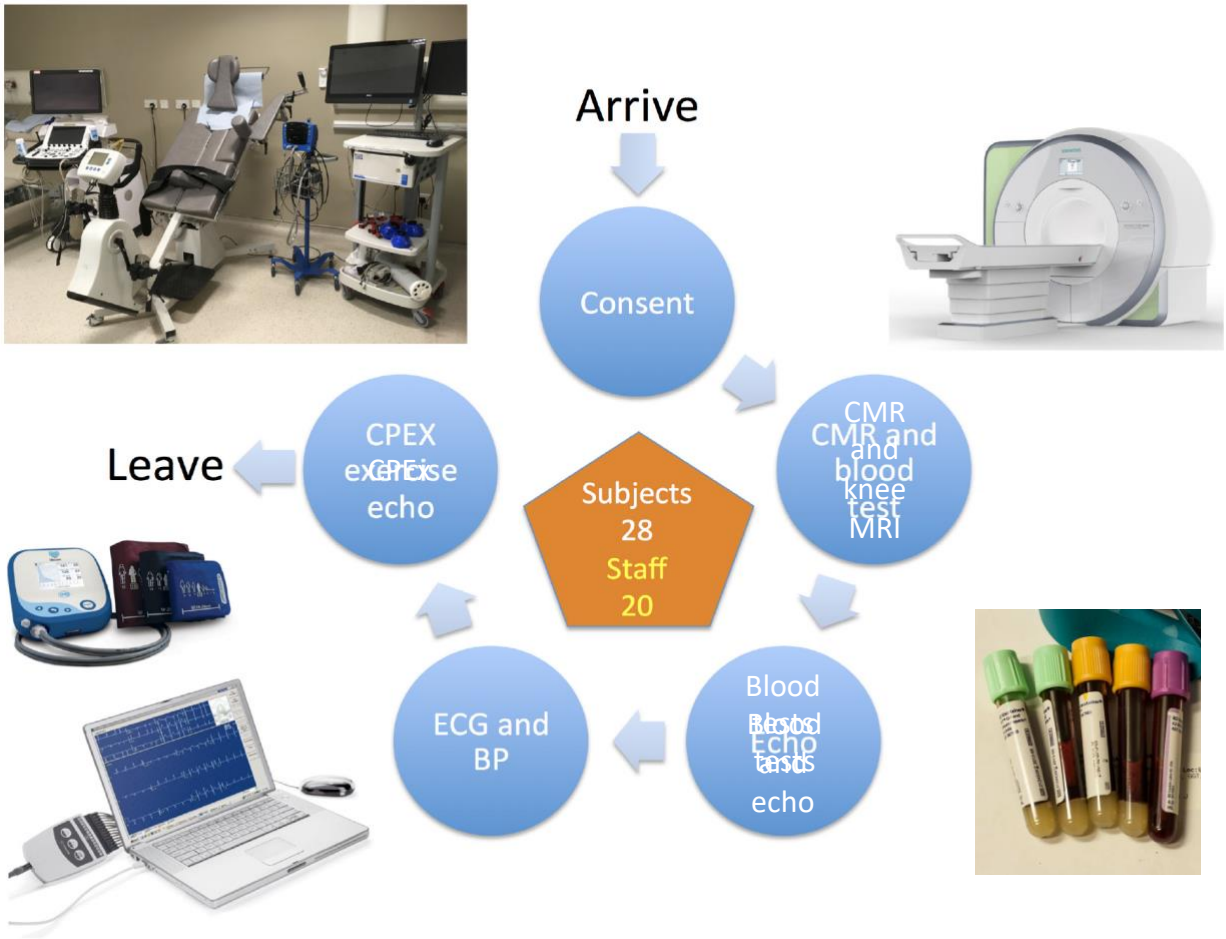

Figure 2 The study visit testing circuit, adapted from D'Silva et al. [76] BP, blood pressure; CMR, cardiac magnetic resonance; CPEX, cardiopulmonary exercise test; ECG, electrocardiogram; MRI, magnetic resonance imaging.

Study Procedures

Allometry, Bioimpedance, and Blood Pressure

Height was recorded using a standard stadiometer. Weight and body fat percentage were measured using digital bioimpedance scales (BC-418, Tanita, United States). Peripheral and central blood pressure (BP) were measured after 5 min of rest in accordance with international standards, [55] supra-systolic oscillometric BP was measured in both arms over 10 s at 200 Hz in a semi-supine position using a Cardioscope II BP C device (USCOM, Sydney, NSW, Australia), which employs an upper arm cuff, as previously described. [56] An ensemble averaged central pressure estimate was derived from the brachial BP and supra-systolic arterial waveforms to estimate central systolic and diastolic BP. At baseline, if the right arm BP was > 10 mmHg greater than the left arm this was used, otherwise the left arm BP was used, and repeated measurements of BP used the same arm as the baseline measurement. All BP measurements were recorded by the same investigator supported by one of five cardiac research nurses working a rotational day schedule.

Systemic vascular resistance (SVR) and systemic aortic compliance (SAC) were calculated as follows:

$$SVR = \frac{MAP}{CO} * 80$$

$$SAC = \frac{SV}{SBP - DBP}$$

Where SVR: systemic vascular resistance; MAP: mean arterial pressure; CO: cardiac output (obtained from cardiac magnetic resonance); SAC: systemic arterial compliance, SBP: systolic BP; DBP: diastolic BP.

Cardiac Magnetic Resonance

CMR is currently the gold standard for non-invasive volumes and mass calculation and tissue characterisation. CMR scans were performed using two 1.5 T magnets (Aera, Siemens Medical Solutions). LV and RV function, volumes, and myocardial mass (excluding papillary muscles) were assessed by cine steady-state free precession sequences and analysed by a single investigator using Circle CVI42 (Circle Cardiovascular Imaging Inc., Calgary, Canada) semi-automated software. Left and right atrial EDV and ESV were derived by manually tracing endocardial atrial contours; maximum and minimum atrial volumes were calculated with a biplanar method, as previously described. [57] Studies were performed by five experienced radiographers and five experienced clinical research fellows working a rotational day schedule. Late gadolinium enhancement (LGE) images were obtained 10 min after the intravenous bolus injection of 0.1 mmol/kg gadolinium-based contrast (gadoterate meglumine, Dotarem, Guerbet, LLC).

CMR: parametric Mapping for Myocardial Tissue Characterisation - T1 and Extra Cellular Volume

Mid-ventricular short-axis pre- and post-contrast (15 min post 0.1 mmol/kg Dotarem) T1 maps were acquired by Modified Look-Locker Inversion recovery (MOLLI) sequence [pre: 5s(3s)3s, post: 4s(1s)3s(1s)2s]. MOLLI T1 maps with motion correction were used to generate automated synthetic extracellular volume (ECV) maps with contours in the mid-anteroseptum used for analysis, as previously described. [58]

Mid-ventricular short-axis T2 maps were acquired with the mean segmental pixel value calculated from a region of interest drawn in the mid-anteroseptum. The choice of using synthetic automated ECV instead of automated ECV depended on the 2016 cyberattack against NHS. In fact, it happened on a Friday afternoon and part of our study follow-up took place on the following weekend. Since the laboratory was down for the whole weekend and blood storage for haematocrit analysis is not possible, follow up haematocrits (and thus ECV) were missing. For this reason, we calculated synthetic ECV, which has a good correlation with normal ECV and does not require haematocrit.[58]

CMR: aortic stiffness and pulse wave velocity

Aortic properties were measured as already described. [35] Briefly, single-shot electrocardiography - gated white blood sagittal aortic ("candy cane") views were acquired first to measure 3- dimensional 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, electrocardiography-gated, and segmented with the following parameters: acquired temporal resolution 9.2 ms (reconstructed to 100 cardiac phases per RR interval); spatial resolution 1.97 x 1.77 mm2; slice thickness 6 mm; through-plane velocity encoding 150 cm/s; field of view 192 x 108 mm; flip angle 20°. The contours for the ascending, proximal, and distal (diaphragmatic) descending aorta were traced semiautomatically using validated software (ArtFun, Inserm, Paris, France) on the phase-contrast modulus for area analysis and velocity images to derive velocity profiles (

Figure 3). [59] 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. [60]

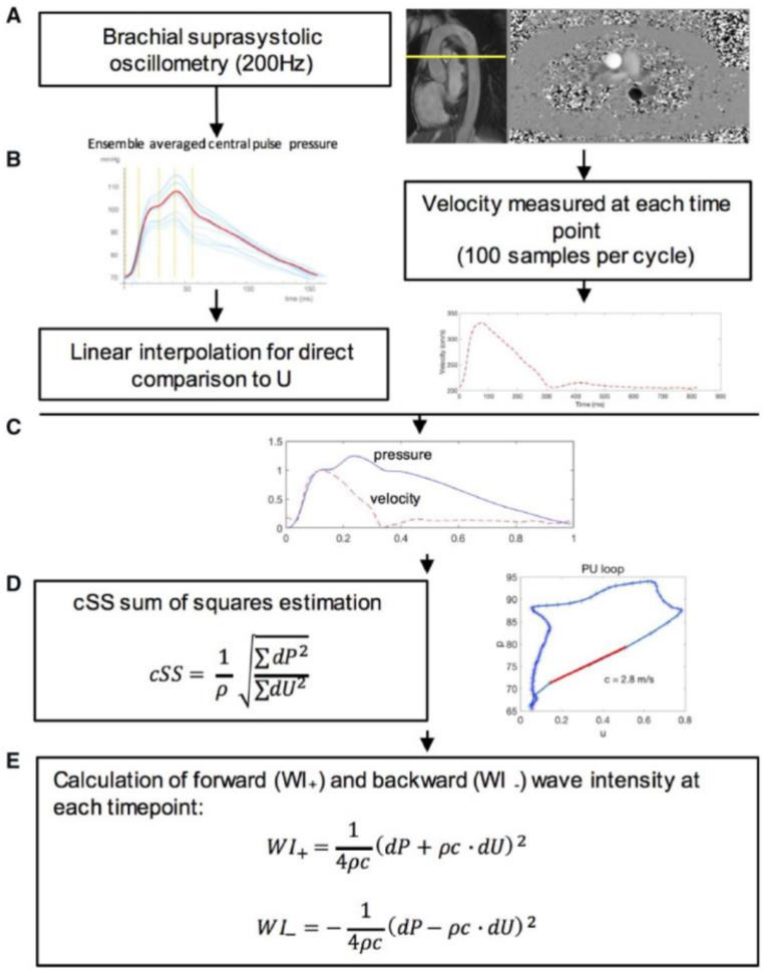

Figure 3. From Bhuva et al. [35] Analysis of blood pressure and CMR-derived velocity data. (A) After a period of rest the patient underwent oscillometric brachial blood pressure on two occasions immediately prior to MRI. A Pulsecor BPfl device acquired 10 s of brachial waveforms at 200Hz. After, phase-contrast MRI was acquired at the level of the pulmonary artery using a free-breathing ECG-gated sequence, acquired at c.100Hz at 60 bpm. (B) A single ensemble averaged central pressure (P) was estimated and velocity (U) measured at each timepoint. (C) Data were aligned by waveform foot to foot. (D) Wave speed measured in early systole using the pressure-velocity loop and sum of squares method after the application of a Savitzky–Golay filter. (E) Wave intensity calculated using the derivatives of pressure and velocity. q, density of blood (1050 kg/m3); c, P-U derived wave speed; cSS, sum of squares estimated c.

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 3 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, the ß-stiffness index was also calculated. This is a pressure-independent measure of intrinsic arterial stiffness because it accounts for the nonlinear compliance to pressure relationship:

$$Distensibility = \frac{A_{\max} - A_{\min}}{A_{\min} \times cPP \times 1000} 10^{-3} \bullet mm\,Hg^{-1}$$

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

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

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 100 mm Hg. 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. [61] 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.

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.[62] Aortic stiffness is strongly correlated with chronological age, so any deviations from expected values may reflect between-subject susceptibility to accelerated ageing or, conversely, vascular adaptation.

CMR: images analysis

All resting imaging studies were analysed by two accredited, experienced cardiologists, blinded to subject identity and time point; 15 CMR studies were randomly selected and re-analysed independently by another experienced cardiologist for assessment of inter-observer variability (

Table 1). Cardiopulmonary exercise test and aortic pulse wave velocity were analysed by two experienced investigators.

	Intraclass correlation coefficient
LV EDV	0.979
LV ESV	0.944
LV EF	0.847
LV mass	0.898
RV EDV	0.929
RV ESV	0.943
RV EF	0.844

Table 1: Reproducibility of Cardiovascular Magnetic Resonance. Intraclass correlation coefficient 0.75 corresponds to an "excellent" agreement rate. LV: left ventricle. EDV: End-diastolic volume; ESV: End-systolic volume; EF: ejection fraction; RV: right ventricle.

Blood Samples

Non-fasting blood samples were collected into standard ethylenediaminetatraacetic acid (EDTA) and serum separating blood collection tubes during intravenous cannulation prior to CMR. On-site laboratory analysis included full blood count and a renal chemistry sample, including creatinine and electrolytes. The remainder of whole blood and serum samples were saved in cryovials and stored at -80°C in refrigerators at St George's, University of London and University College London.

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing was performed using a semi-recumbent tilting cycle ergometer (Schiller ERG 911 BP/LS, Schiller, Switzerland) with an incremental ramp protocol of 15–30 W/min, based on a pre-specified algorithm incorporating subject height and gender. Subjects were exercised to volitional exhaustion with continuous ECG monitoring. Maximal effort was assessed by the presence of a plateau in oxygen uptake seen in Wasserman Plot panel 3, respiratory exchange ratio (RER) > 1.15 and subject perceived exhaustion, as recognised parameters of assessment of effort. [63] Achievement of maximal predicted heart rate was a less reliable marker of maximal effort with testing conducted on a semi-recumbent cycle, as compared to a treadmill. Breath-by-breath pulmonary gas exchange and ventilation were continuously measured by metabolic cart (Quark

CPET, COSMED, Rome, Italy), as previously described. [64] The ventilatory threshold was determined by the V-slope method, where two intersecting lines were drawn using dedicated software (Omnia, COSMED, Rome, Italy) on the VCO_2 vs VO_2 Wasserman Plot panel 5. To fully characterize exercise ability and potential using the semi-recumbent ergometer, both maximal (maximal VO_2 and percentage predicted maximal VO_2) and submaximal indices [oxygen uptake efficiency slope (OUES)] were assessed. In order to appropriately classify cardiorespiratory trainability by accounting for the random within-individual variation and measurement error, a combination of the technical error of measurement (TEM) and the minimal clinically important difference (MCID) were incorporated, as previously described. [65] Studies were performed by four experienced cardiac physiologists working a rotational day schedule and analysed by two investigators. Target exercise times were 5–12 minutes, if a subject at baseline exercised for more than 12 min to volitional exhaustion the ramp protocol was increased by 5 W/min on post-marathon testing.

Knee Magnetic Resonance Imaging

Runners recruited during the second year of the study with no present knee injury/history of knee injury also underwent an orthopaedic assessment consisting of knee MRI and the administration of the Knee Injury and Osteoarthritis Outcome Score (KOOS), as a self-reported questionnaire of the knee condition and associated injuries that can result in osteoarthritis. [66] The assessment is divided into five categories: pain, other symptoms, function in daily living, knee-related quality of life and function in sport and recreation. Participants were asked to complete the questionnaire both before and after the marathon to assess their perceived knee joint health. Each question was provided with five potential answers and marked from zero to four. The sum of the scores from each category was converted into a 0–100 scale, with zero indicating extreme knee problems and 100 indicating no knee problems.

Knee MRI was performed using a 3.0T magnet (Prisma, Siemens Medical Solutions, Erlangen, Germany) and dedicated knee coil. The imaging protocol included proton density-weighted fat

suppressed (PD FS) sequences in axial [repetition time (TR) msec/echo time (TE) msec; 4630/37], sagittal (4200/41 ms) and coronal planes (5240/41 ms). All slices were 3 mm thick, with an image size/acquisition matrix of 320×320 pixels. The total acquisition time per bilateral scans was 25 min. All MR images were reviewed using a picture archiving and communications system workstation by a musculoskeletal radiologist with 10years experience at consultant level. 30% of the cohort, randomly selected, were additionally and independently evaluated, by a second fellowship-trained musculoskeletal radiologist with 9years experience at consultant level. The two examiners were blinded to the baseline characteristics of the volunteers. Images of both time points were separately analysed. In case of discrepancies between the radiologists' evaluation, consensus scores were achieved after consultation. Findings of the knee joint from MRIs were analysed using different validated scoring systems for the presence of any signal changes/lesions of varying severity: menisci, cartilage, bone marrow, tendons, ligaments. [67], [68], [69] Other findings were also specified, using a binary scoring system. [70] See

Table 2.

Knee feature	Grading system
Meniscus	Modified BLOKS [67] and ACLOAS [71]†
Cartilage	Modified Noyes and Stabler [53], [72]††
Bone marrow	KOSS [69]
Tendons	Johnson DP et al. [73] †††
Ligaments	ACLOAS [71]
Joint effusion	WORMS [74]
Synovial collections*	Binary—MOAKS [75]
Iliotibial band	Binary—MOAKS [75]
Cysts**	Binary

*Table 2: BLOKS, Boston Leeds Osteoarthritis Knee Score; ACLOAS, Anterior Cruciate Ligament OsteoArthritis; KOSS, Knee Osteoarthritis Scoring System; WORMS, Whole-Organ Magnetic Resonance Imaging Score; MOAKS, MRI Osteoarthritis Knee Score. *Synovial collections: prepatellar bursitis, pes anserine bursitis, Hoffa's synovitis; **cysts: Baker's cyst, other ganglion cysts. † Both horns of the meniscus were assessed, except for the body. ††A modified Noyes system on a scale 0–4 used by several papers was included here. ††† Scoring system primarily designed for the patellar tendon and was adjusted to include other tendons. Binary scoring system was defined as present/absent.*

All abnormalities were recorded including Grade 1 abnormalities (all scores/grades different from zero were defined as 'lesions' throughout the text). In addition, we analysed the presence/absence of meniscal tears prior to the run versus the participants' marathon finishing times, to understand whether the presence of asymptomatic meniscal tears affected their performance.

For assessment purposes, the patella was divided anatomically into medial and lateral regions, with the ridge being considered as part of the medial region. The tibia was divided into medial and lateral regions and the femur was divided into medial, lateral and trochlea regions and the trochlea was further divided into medial, central, lateral. The medial and lateral menisci were each divided into two subregions: anterior horn and posterior horn. Scores were assigned for each individual region.

Finally, runners were invited to have another knee MRI scan after 6 months from the marathon (same protocol).

Statistical Analysis

Quantitative variables are expressed as mean ± standard deviation (SD) or median (interquartile range) for skewed data and categorical variables as an absolute number with percentage in parentheses. T-test (or Wilcoxon test) and chi-square test were used to compare continuous variables and categorical variables between groups respectively. Moreover, baseline and follow-up data of the same group were compared using paired Student's t-tests for normally distributed or the Wilcoxon signed rank sum test for nonnormally continuous variables, respectively.

All tests were 2-tailed, and a p value <0.05 was considered statistically significant. The analyses were performed using R Core Team software (2018), Vienna, Austria.

Cardiovascular remodelling analysis

For the cardiovascular analysis the runners were split into two groups: “under 35” (U35) and “over 35” (O35), when a runner is <35 or ≥35 years respectively, accordingly to the clinical definition of “master athlete”. [77]

To assess the cardiovascular effects of aerobic exercises in different age group, we used linear mixed-effects models accounting for repeated measurements with an unstructured covariance matrix, fitting the models by maximizing the restricted log-likelihood followed by a posteriori contrasts when applicable. False Discovery Rate (FDR) algorithm was used for multiple post-hoc comparisons. The variables were transformed to handle possible violations of the hypothesis of normality of the residuals.

Vascular remodelling analysis

Baseline and follow-up data were compared using paired Student’s t-tests for normally distributed continuous variables or the Mann-Whitney U test and chi-square tests for nonnormally distributed and categorical variables, respectively.

To investigate vascular parameters, the runners were a priori stratified by the median age of the cohort (37 years), similar to Tanaka et al. [33] 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 maximal oxygen consumption (peak VO2) were adjusted for age and sex. Associations between aortic stiffness and sex were adjusted for age and peak VO2. Because aortic stiffness is partly dependent on loading conditions, the association between the change in aortic distensibility and change in 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 b-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. For these analyses, the FDR approach was used to determine significant associations.

Knee joint MRI analysis

For post-marathon changes, both knees of the same participant were examined, and each knee was treated independently in the statistical analysis. Unpaired t-test was used to assess any significant differences between the two groups (marathon runners versus pre-race dropouts) with regard to age, BMI and height. Chi-square test was used for comparison of gender differences between the two groups, and of differences between the prevalence of lesions in these groups between baseline and follow up.

Results

Study population

Two hundred and thirty-seven runners were recruited. Among them, 166 (70%) completed the race, 52 (22%) interrupted their training following musculoskeletal injury, 19 (8%) did not compete for other reasons. Among the race completers, 27 did not attend for follow-up, 1 was excluded after being diagnosed with hypertension. The final cohort consisted of 138 subjects who underwent evaluations at 180 ±10 days before the London Marathon and 16 ±8 days after (Figure 4). Baseline mean age was 37 ±10years (range 21-69y.o.), 51% were females (mean age 37 ±10years, 47% <35years), 49% were males (mean age 37 ±11years, 54% <35years). Reported median hours of training per week were 1.9 (Table 3). Among those subjects, 115 runners (51 males, 64 females, median age: 44 years, range: 25–73 years) also underwent the orthopaedic evaluation.

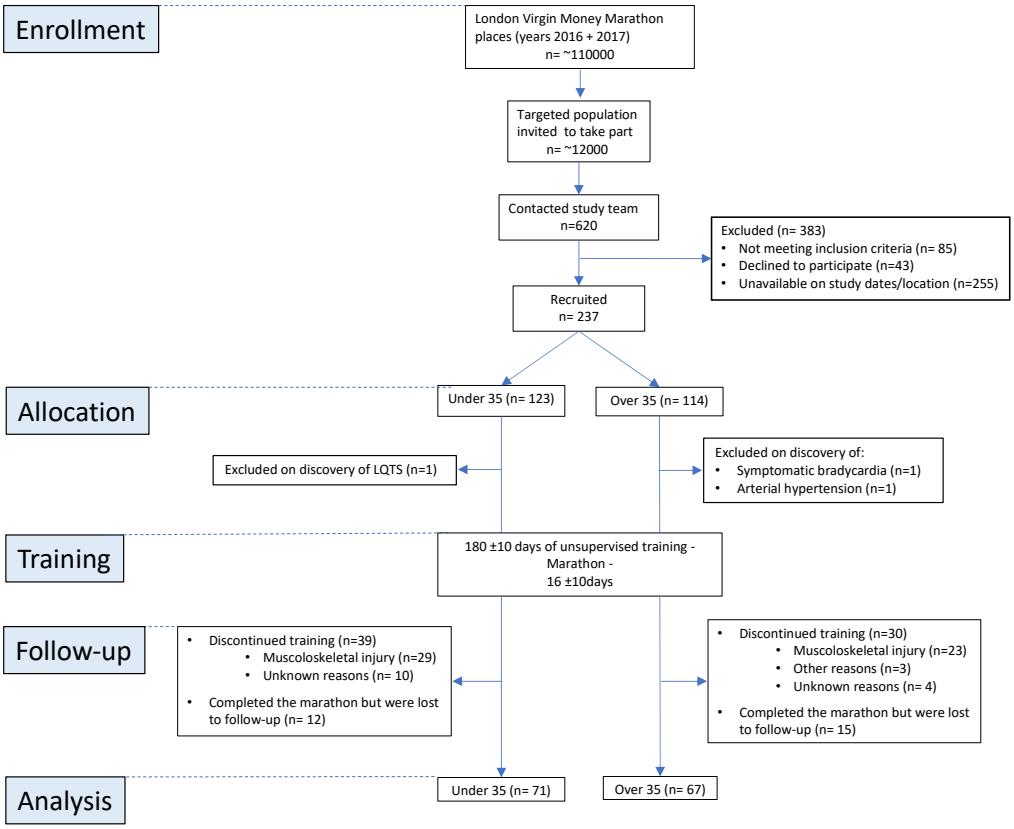

Figure 4: Consort flow diagram illustrating subject recruitment and follow up., From Torlasco et al. [78] LQTS: long QT syndrome; U35: under 35, less than 35 years; O35: over 35, 35 years and older.

Baseline characteristics

Race finishers were similar in age and gender (U35: n=71, mean age 29 ±4y, females=49%; O35: n = 67, mean age 46 ±7y, females = 51%). The prevalence of former smokers was lower in U35 than in O35 (10% vs 32% respectively, p =0.002). No differences were observed for ethnicity and blood tests results (Table 3).

Marathon completion rate and injury rate during training did not differ among age groups (Table 3; Figure 4). Mean race time (HH:MM) was 4:44 (range, faster-to-slower runner: 2:57-7:57) in the whole cohort. U35 were faster (mean race time in U35: 4:38 [range 2:56–6:51] against 5:15 [range 3:27–7:57] in O35). These times exceed those reported for wide cohorts [79] by 9 minutes in U35 against the age group 20-29 years [80] and by 50 minutes for O35 against the age group 40-49 years. However, these average times include professionals and non-first time marathon runners. [80]

	Whole cohort		**U35 (≤34 years)**		**O35 (≥35 years)**	
n	138		71		67	
Age (years)	37	(21-69)	29	±4	46	±7
Female	70	(51%)	34	(49%)	36	(51%)
Male	68	(49%)	37	(54%)	31	(46%)
Ethnicity						
White	125	(91%)	62	(93%)	63	(89%)
Asian	4	(4%)	1	(1%)	3	(4%)
Black	3	(2%)	2	(2%)	1	(1%)
Mixed	4	(3%)	0		4	(5%)
Other	2	(1%)	0		2	(2%)
Smoking						
Non-smoker	102	(74%)	60	(85%)	42	(63%)
Current smoker	7	(5%)	4	(5%)	3	(5%)
Ex-smoker	29	(21%)	7	(10%)	22	(32%)
Exercise / week (hrs)	1.9	(0-10)	1.8	(0-4)	2	(0-10)
Running Time (hrs:mins)	4:44	(2:57 – 7:57)	4:38	(2:56-6:51)	5:15	(3:27 – 7:57)

Table 3: Baseline characteristics of study participants in the final cohort, stratified by age category, adapted from Torlasco et al.[78] Data are expressed as mean (range), mean ±SD or number (%).

Mean height, weight, body surface area (BSA) did not differ between groups. On average, body mass index (BMI) was high-normal (24.4, range 16.7-35.2), and lower in U35 than O35 (U35: 23.6 ±0.3; O35: 25.1 ±0.4, p = 0.009). Table 4.

Cardiopulmonary test

All participants achieved a respiratory quotient (RQ) of 1.1 or greater at the baseline CPET. Age predicted peak oxygen uptake was 109 ±17%, without significant differences between groups. However, absolute physical performance was superior in U35 than in O35 for peak oxygen uptake (+5.6 ml/kg/min, p <0.001), maximal reached power (+13 W, p = 0.012) and exercise time (+166 seconds, p <0.001).

	Whole cohort (n= 138)	**U35 (≤34 years) (n= 71)**	**O35 (≥35 years) (n= 67)**	**p**
Allometry				
Height (cm)	172.9 ± 9.5	174.3 ± 9.5	171.6 ± 9.4	0.09
Weight (kg)	73.2 ± 13	71.8 ± 12	74.5 ± 15	0.1
BMI (Kg/m^2)	24.4 ± 0.3	23.6 ± 0.3	25.1 ± 0.4	0.009
Body Fat (%)	25 ± 8	23 ± 8	27 ± 8	0.021
CPET				
Exercise time (secs)	674 ± 133	594 ± 104	760 ± 104	<.001
Peak VO_2 (ml/kg/min)	34.5 ± 7.5	37.1 ± 6.8	31.4 ± 7	<.001
Peak power (W)	216 ± 57	222 ± 54	209 ± 59	0.012
% of VO_2 max	109 ± 17	106 ± 16	113 ± 18	0.1
Peak HR (bpm)	163 ± 15	168 ± 14	159 ± 16	<.001
Rest HR (bpm)	68 ± 12	73 ± 12	64 ± 14	0.001
RQ	1.22 ± 0.09	1.20 ± 0.09	1.24 ± 0.08	0.01
Peak VE (l/min)	85 ± 24	76 ± 23	93 ± 29	0.2

Table 4: Allometry and CPET baseline tests results for the patients who completed the study: whole sample, U35 and O35. Data are expressed as mean ±SD. P value refers to U35 against O35. BMI: body mass index; HR: heart rate; RQ: respiratory quotient; VE: Pulmonary Ventilation.

Cardiac Magnetic Resonance

At CMR, average biventricular chambers size and LV mass indexed for BSA were normal in the whole sample. [81] All volumes and mass were higher in U35 than in O35 (LV EDVi: +8 ml/m^2; LV ESVi: +5 ml/m^2, RV EDVi and ESVi: +10 ml/m^2; LV mass +6 gr/m^2; p<0.001 for all). Native T1 values and synthetic ECV were within the normal range and not different between groups. [82] There was basal inferior-lateral mid-myocardial non-ischemic LGE in one male subject in the O35, both before and after training (unchanged). See Table 5.

	Whole cohort (n= 138)	U35 (≤34 years) (n= 71)	O35 (≥35 years) (n= 67)	p
CMR				
LV EDV i (ml/m^2)	86 ± 14	90 ± 14	82 ± 13	<.001
LV ESV i (ml/m^2)	30 ± 7	33 ± 8	28 ± 6	<.001
SV i (ml/m^2)	56 ± 10	58 ± 10	54 ± 9	0.008
LV EF (%)	0.65 ± 0.05	0.64 ± 0.05	0.66 ± 0.05	0.001
CO (l/min)	6.7 ± 1.6	7.1 ± 1.7	6.3 ± 1.5	0.003
LV mass i (g/m^2)	62 ± 12	65 ± 12	59 ± 12	<.001
LV mass/volume ratio	0.72 ± 0.1	0.71 ± 0.1	0.73 ± 0.1	0.049
RV EDV i (ml/m^2)	88 ± 15	92 ± 15	82 ± 13	<.001
RV ESV i (ml/m^2)	35 ± 10	39 ± 9	29 ± 8	<.001
RV SV i (ml/m^2)	53 ± 9	53 ± 10	53 ± 9	0.9
RV EF (%)	0.61 ± 0.06	0.58 ± 0.05	0.65 ± 0.07	<.001
LAV i (ml/m^2)	51 ± 29	51 ± 28	50 ± 31	0.8
Native myocardial T1 (msec)	1009 ± 29	1009 ± 28	1009 ± 28	0.4
Synthetic ECV (%)	26.3 ± 3	25.8 ± 3	26.7 ± 3	0.1

Table 5: CMR baseline tests results for the patients who completed the study: whole sample, U35 and O35. Data are expressed as mean ±SD. P value refers to U35 against O35. LV: left ventricle. EDV: end diastolic volume. ESV: end systolic volume. SV: stroke volume. EF: ejection fraction. CO: cardiac output. RV: right ventricle. LAV: left atrium volume. ECV: extra cellular volume.

Blood pressure and vascular properties

Blood pressure and Average BP was normal in the whole sample, but lower in U35 than in O35 by 5/3 mmHg for brachial SBP/DBP (p = 0.02/0.03 respectively) and by 6/3 mmHg for central SBP/DBP (p = 0.004 for cSBP and p = 0.03 for cDBP). Table 6.

Arterial PWV in the whole aorta was 6±15m/s, lower in U35 than O35 by 1.4m/sec (p <0.001).[35] SVR were on average 1135dyn·s/cm^5, significantly lower in U35 than in O35 by 173dyn·s/cm^5 (p <0.001). Table 6.

SAC of the whole sample was 3.0 ±8 ml/m^2, higher in U35 than in O35 (+0.3 ml/m^2, p=0.001). 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 x 10^{-3} mm Hg^{-1} and an increase in ß-stiffness by 27%, 22%, and 16%, respectively. Table 6.

	Whole cohort (n= 138)	U35 (≤34 years) (n= 71)	O35 (≥35 years) (n= 67)	p
Blood Pressure				
Heart Rate (bpm)	70 ± 13	71 ± 13	69 ± 13	0.9
Brachial SBP (mmHg)	121 ± 14	119 ± 11	124 ± 15	0.026
Brachial DBP (mmHg)	75 ± 7	73 ± 5	76 ± 8	0.020
Central SBP (mmHg)	112 ± 13	109 ± 11	115 ± 14	0.004
Central DBP (mmHg)	76 ± 7	75 ± 5	78 ± 8	0.030
Central MAP (mmHg)	87 ± 8	86 ± 7	91 ± 10	0.009
Pulse Wave Analysis				
PWV Arch (m/s)	4.7 ± 1.4	3.9 ± 0.6	5.6 ± 1.6	<.001
PWV Descending aorta (m/s)	8.3 ± 2.5	8.2 ± 2.6	8.5 ± 2.3	0.060
PWV Whole aorta (m/s)	6.0 ± 1.5	5.3 ± 1	6.7 ± 1.7	<.001
SAC (ml/m²)	3.0 ± 0.8	3.2 ± 0.7	2.9 ± 0.9	0.001
SVR (dyn·s/cm^5)	1135 ± 262	1052 ± 239	1225 ± 275	0.001

Table 6: BP and vascular properties baseline tests results for the patients who completed the study: whole sample, U35 and O35. Data are expressed as mean ±SD. P value refers to U35 against O35. BMI: body mass index. SBP: systolic blood pressure. DBP: diastolic blood pressure. MAP: mean arterial pressure. PWV: pulse wave velocity. SAC: systemic arterial compliance. SVR: systemic vascular resistances.

Follow up

Cardiopulmonary exercise testing

After training, there were small increases in overall fitness. Mild improvement was observed in peak oxygen uptake (+1 ml/kg/min, p = 0.035). Exercise time increased on average by 21 seconds (p = 0.010) and peak power by 4W (p = 0.002). Subgroup analysis showed these changes in the U35 only (exercise time: +6%, peak power: +5%, peak VO_2 +3%; p <0.01, p <0.01 and p <0.05 respectively). Resting heart rate was unchanged at follow-up. See Table 7.

Allometry

After training, weight fell by 900g (p = 0.001) and body fat by 1% (p=0.006) driven by O35 (on average -2%, p <0.001). Height decreased by 6 mm in both groups. See Table 7.

Cardiac remodelling

After training, biventricular volumes increased by an average of 2 ml/m^2 (EDVi) and 1 ml/m^2 (ESVi) (p <0.05 for both). At post hoc analysis, the chambers size increase was observed only in the U35 (LVEDVi: +3%, LVESVi: +8%, RVEDVi: +4%, RVESVi: +5%, p <0.001 for all), while no change was observed in O35. A similar 4% (~3 g/m^2) increase in LV mass was observed in both groups (p<0.001) representing mild concentric remodelling (LV mass/volume ratio increase of 0.2), driven by O35, in whom LV mass/volume ratio went from 0.73±0.1 to 0.76±0.1 (p=0.001).

Synthetic ECV and native myocardial T1 mapping were unchanged after training. No changes were observed in the myocardial partition coefficient, post-contrast T1 myocardial, full blood count or kidney function in either group.

See Table 7 and Table S 1.

		Whole cohort		U35 (≤34 years)		O35 (≥35 years)		p condition	p age	p interaction
Allometry	**Time point**									
Height (cm)	Baseline	172.9 ± 9.5		174.3 ± 9.5		171.6 ± 9.4		0.001	0.09	-
	Follow-up	172.4 ± 9.5		173.7 ± 9.5	*	171.0 ± 9.5	**			
Weight (kg)	Baseline	73.2 ± 13		71.8 ± 12		74.5 ± 15		0.001	0.1	0.04
	Follow-up	72.3 ± 12		71.4 ± 10		73.1 ± 14	**			
BMI	Baseline	24.4 ± 0.3		23.6 ± 0.3		25.1 ± 0.4	§§	0.1	0.009	0.08
	Follow-up	24.2 ± 0.3		23.6 ± 0.3		24.8 ± 0.4	§			
Body Fat (%)	Baseline	25 ± 8		23 ± 8		27 ± 8		0.006	0.021	0.06
	Follow-up	24 ± 9		23 ± 9		26 ± 9				
Blood Pressure										
Heart Rate (bpm)	Baseline	70 ± 13		71 ± 13		69 ± 13		-	-	-
	Follow-up	68 ± 12		68 ± 12		68 ± 13				
Brachial SBP (mmHg)	Baseline	121 ± 14		119 ± 11		124 ± 15	§§	<.001	0.026	0.049
	Follow-up	117 ± 13		116 ± 10	*	118 ± 15	***			
Brachial DBP (mmHg)	Baseline	75 ± 7		73 ± 5		76 ± 8	§§	<.001	0.020	0.028
	Follow-up	72 ± 7		72 ± 5		73 ± 8	***			
Central SBP (mmHg)	Baseline	112 ± 13		109 ± 11		115 ± 14	§§	<.001	0.004	0.043
	Follow-up	108 ± 13		106 ± 10		109 ± 15	***			
Central DBP (mmHg)	Baseline	76 ± 7		75 ± 5		78 ± 8	§§	<.001	0.030	0.011
	Follow-up	74 ± 7		73 ± 5	*	74 ± 8	***			
Central MAP (mmHg)	Baseline	87 ± 8		86 ± 7		91 ± 10	§§	<.001	0.009	0.016
	Follow-up	85 ± 10		84 ± 7	*	86 ± 10	***			

Pulse Wave Analysis														
PWV Arch (m/s)	Baseline	4.7	±	1.4	3.9	±	0.6		5.6	±	1.6	§§§	0.2	<.001	-
	Follow-up	4.6	±	1.2	3.9	±	0.6		5.3	±	1.3				
PWV Descending aorta (m/s)	Baseline	8.3	±	2.5	8.2	±	2.6		8.5	±	2.3		0.1	0.060	-
	Follow-up	7.9	±	2.4	7.6	±	4.9		8.2	±	2.5				
PWV Whole aorta (m/s)	Baseline	6.0	±	1.5	5.3	±	1		6.7	±	1.7	§§§	0.038	<.001	-
	Follow-up	5.7	±	1.4	5.1	±	0.7		6.5	±	1.7				
SAC ml/m²	Baseline	3.0	±	0.8	3.2	±	0.7		2.9	±	0.9	§§	0.022	0.001	-
	Follow-up	3.2	±	0.7	3.4	±	0.7		3	±	0.7	§§			
SVR dyn·s/cm^5	Baseline	1135	±	262	1052	±	239		1225	±	275		0.034	0.001	-
	Follow-up	1092	±	246	1029	±	255		1160	±	239				
CMR														
LV EDV i (ml/m^2)	Baseline	86	±	14	90	±	14		82	±	13	§§	0.014	<.001	0.027
	Follow-up	88	±	14	93	±	15	**	82	±	13	§§§			
LV ESV i (ml/m^2)	Baseline	30	±	7	33	±	8		28	±	6	§§	0.019	<.001	0.023
	Follow-up	31	±	8	35	±	8	**	28	±	7	§§§			
SV i (ml/m^2)	Baseline	56	±	10	58	±	10		54	±	9	§	-	0.008	-
	Follow-up	57	±	9	59	±	10		54	±	8				
LV EF	Baseline	0.65	±	0.05	0.64	±	0.05		0.66	±	0.05	§	-	0.001	-
	Follow-up	0.64	±	0.05	0.63	±	0.05		0.66	±	0.05				
CO (l/min)	Baseline	6.7	±	1.6	7.1	±	1.7		6.3	±	1.5	§	-	0.003	-
	Follow-up	6.6	±	1.7	7	±	1.8		6.1	±	1.5				
LV mass i (g/m^2)	Baseline	62	±	12	65	±	12		59	±	12		<.001	<.001	-
	Follow-up	65	±	13	68	±	12	***	62	±	13	***			
LV mass/volume ratio	Baseline	0.72	±	0.1	0.71	±	0.1		0.73	±	0.1		0.001	0.049	0.06
	Follow-up	0.74	±	0.1	0.73	±	0.1		0.76	±	0.1	**			
RV EDV i (ml/m^2)	Baseline	88	±	15	92	±	15		82	±	13		0.001	<.001	-
	Follow-up	90	±	16	96	±	17	**	85	±	14				
RV ESV i (ml/m^2)	Baseline	35	±	10	39	±	9		29	±	8		0.001	<.001	-
	Follow-up	36	±	11	41	±	10	**	31	±	9				

RV SV i (ml/m^2)	Baseline	53	±	9	53	±	10		53	±	9		0.08	0.9	-
	Follow-up	54	±	9	55	±	9		54	±	8				
RV EF	Baseline	0.61	±	0.06	0.58	±	0.05		0.65	±	0.07	§§§	0.4	<.001	-
	Follow-up	0.61	±	0.05	0.57	±	0.05		0.64	±	0.07				
LA volume i (ml/m^2)	Baseline	51	±	29	51	±	28		50	±	31		-	-	0.09
	Follow-up	50	29		48	±	26		52	±	31				
Native myocardial T1 (msec)	Baseline	1009	±	29	1009	±	28		1009	±	28		-	-	-
	Follow-up	1006	±	33	1006	±	33		1006	±	33				
Synthetic ECV	Baseline	26.3	±	3	25.8	±	3		26.7	±	3		-	-	-
	Follow-up	26.3	±	3	26	±	3		26.6	±	3				
CPET															
Exercise time (secs)	Baseline	674	±	133	594	±	104		760	±	104		0.01	<.001	0.037
	Follow-up	695	±	127	630	±	115	**	764	±	100				
Peak VO_2 (ml/kg/min)	Baseline	34.5	±	7.5	37.1	±	6.8		31.4	±	7		0.035	<.001	-
	Follow-up	35.6	±	8.3	38.5	±	8	*	31.9	±	7				
Peak power (W)	Baseline	216	±	57	222	±	54		209	±	59		0.002	0.012	0.001
	Follow-up	220	±	60	232	±	59	**	208	±	60				
% of VO_2 max	Baseline	109	±	17	106	±	16		113	±	18		-	-	-
	Follow-up	113	±	19	110	±	17		116	±	21				
Peak HR (bpm)	Baseline	163	±	15	168	±	14		159	±	16		-	<.001	0.07
	Follow-up	165	±	15	173	±	15		158	±	14				
RQ	Baseline	1.22	±	0.09	1.20	±	0.09		1.24	±	0.08	*	0.02	0.01	-
	Follow-up	1.21	±	0.08	1.19	±	0.10		1.21	±	0.07				

*Table 7: Baseline and post-marathon tests results for the whole sample, U35 and O35. Values are n, median (interquartile range), mean ±SD. Only p values that are significant at 0.10 false discovery rate are reported. * = p pre vs post <0.05; ** = p pre vs post <0.01; *** = p pre vs post <.001; § = p U35 vs O35 <0.05; §§ = p U35 vs O35 <0.01; §§§ = p U35 vs O35 <.001. BMI: body mass index. SBP: systolic blood pressure. DBP: diastolic blood pressure. MAP: mean arterial pressure. PWV: pulse wave velocity. SAC: systemic arterial compliance. SVR: systemic vascular resistances. LV: left ventricle. EDV: end diastolic volume. ESV: end systolic volume. SV: stroke volume. EF: ejection fraction. CO: cardiac output. RV: right ventricle. LA: left atrium. ECV: extra cellular volume.*

Blood pressure, systemic haemodynamics and vascular remodelling.

Training reduced BP, with the largest falls observed in O35. Brachial SBP/DBP dropped by 3/1mmHg in U35 ($p = 0.030$ for SBP, $p = 0.08$ for DBP) and by 6/3mmHg in O35 ($p<0.001$ for both SBP and DBP); central SBP/DBP dropped by 3/2mmHg in U35 ($p=0.05$ for SBP, $p=0.004$ for DBP) and dropped by 6/4mmHg in O35 ($p<0.001$ for both SBP and DBP). There was a mean 4% decrease in SVR after training ($p = 0.04$), driven by O35 (baseline vs follow-up in U35: $p = 0.31$; O35: $p = 0.060$), associated with a 7% reduction in SAC ($p = 0.020$), similar in U35 and O35 (baseline vs follow-up $p = 0.002$ for both).

See Figure 5, Table 7 and Table S 1.

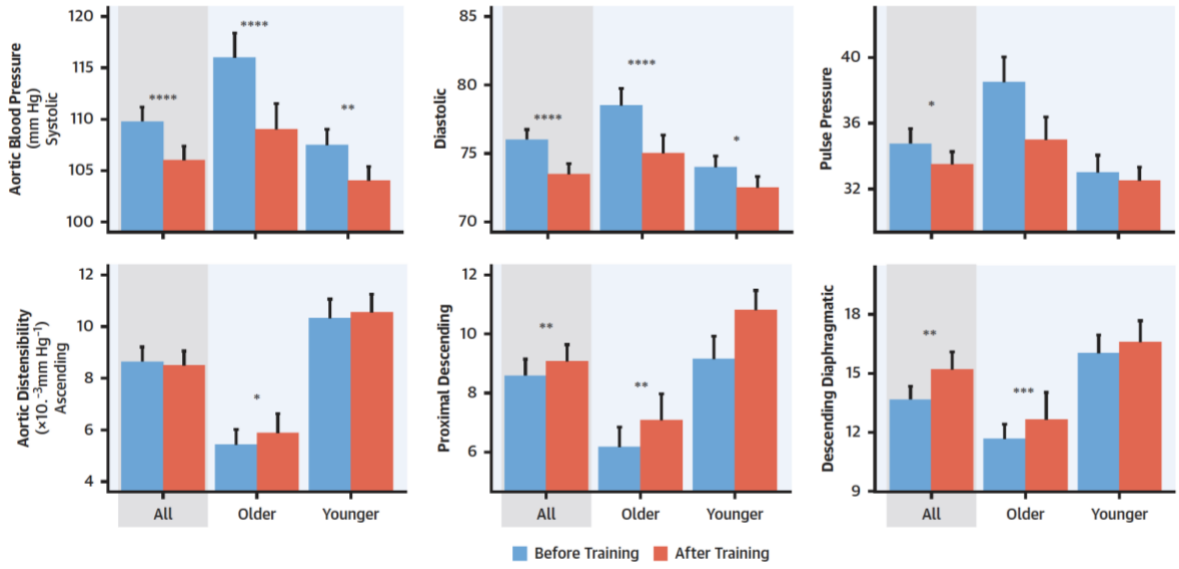

*Figure 5 from Bhuva et al. [62] Greater Change With Exercise Training in Aortic Blood Pressure and Distensibility Is in Older Age Category Participants (Age >37 Years). (Top left to top right) Aortic blood pressure—systolic, diastolic, and pulse pressures. (Bottom left to bottom right) Aortic distensibility—ascending, proximal descending, and descending diaphragmatic. Data are means and standard errors. *p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001.*

Aortic stiffness reduced with training and was more pronounced in the distal aorta (Table 8). 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 $p = 0.002$, respectively). The change in distensibility was independent of the change in mean arterial pressure ($p < 0.001$ for the descending aorta).

ß-stiffness showed less pronounced but similar regional trends. ß-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 1). The change in ß-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.

See Table 8.

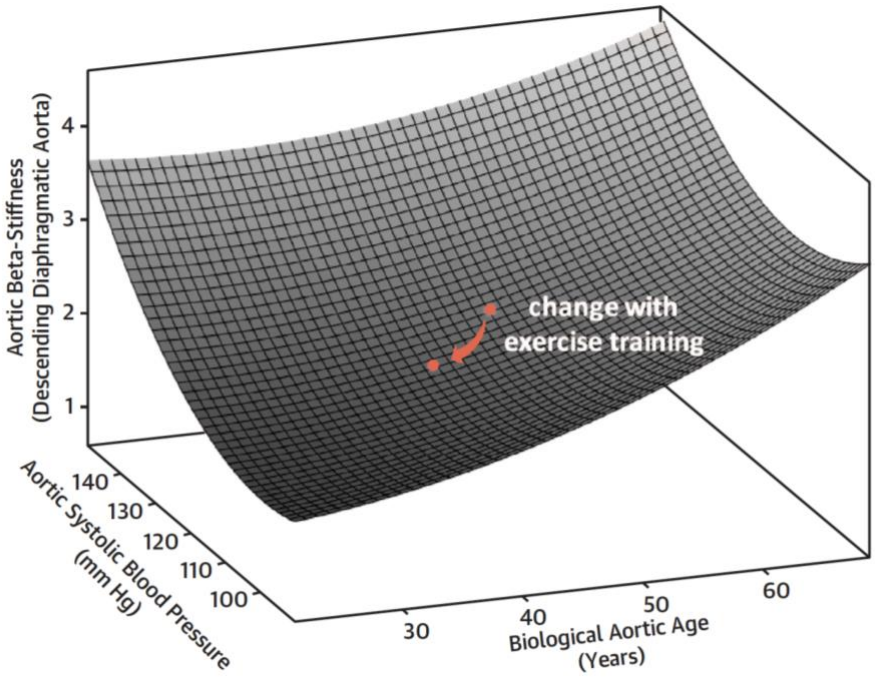

Figure 6: from Bhuva et al. [62]Baseline Central (Aortic) Systolic Blood Pressure, Aortic Stiffness, and Estimated Aortic Age. The red arrow shows the change with exercise training for the average older marathon completer.

After training, the increase in distensibility translated to a reduction in biological aortic age by 1.5 years (95% CI: -0.9 to 5.4 years; p = 0.16), 3.9 years (95% CI: 1.1 to 7.6 years; p = 0.009) and 4.0 years (95% CI: 1.7 to 8.0 years; p = 0.002) in the ascending, proximal descending, and diaphragmatic descending aorta, respectively. When estimated from ß-stiffness, biological aortic age reduced by 0

years (95% CI: -2.8 to 2.8 years; p = 0.99), 2.4 years (95% CI: -0.5 to 5.3 years; p = 0.11), and 3.2 years (95% CI: 0.1 to 6.2 years; p = 0.04) in the ascending, proximal descending, and diaphragmatic descending aorta, respectively.

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 8, Figure 5). Men had a greater reduction than women in descending aorta ß-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 ß-stiffness of the proximal and diaphragmatic descending aorta ($r_{partial}$ 0.23 and 0.21; p = 0.006 and p = 0.02, respectively). The strength of these associations was reduced when adjusted for age and sex ($r_{partial}$ 0.16 and 0.20; p = 0.06 and p = 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). 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). There was no association with the change in ß-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.

	Whole Cohort			Older (Age >37 years)			Younger (≤ 37 years)		
	Baseline	Follow up	P Value	Baseline	Follow up	P Value	Baseline	Follow up	P Value
N	138			59			79		
Distensibility (x 10^{-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)	9.2 (8-14)	-
Diaphragmatic Descending	13.7 (11-18)	15.2 (12-21)	0.002	11.7 (9-14)	12.7 (10-17)	<.001	16.0 (13-20)	16.0 (13-20)	-
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)	2.7 (2.1-2.9)	-
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)	2.7 (2.2-3.4)	-
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 (1.6-2.1)	-
Vascular Age (distensibility)									
Ascending	39.3 (28-53)	39.9 ±16.9	-	53.1 (37-59)	51.2 (37-59)	0.04	32 (20-40)	31.0 (19-44)	-
Proximal Descending	40.0 (22-55)	34.8 ±19.0	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)	33.6 ±18.6	0.002	47.8 (41-57)	44.6 (32-53)	<.001	33.6 (20-44)	31.8 (12-41)	-
Vascular Age (beta-stiffness)									
Ascending	38.3 ±17.9	4.2 (4-5)	-	50.1 ±17.7	48.5 ±17.2	-	29.4 ±11.9	30.9 ±11.6	-
Proximal Descending	37.1 ±20.5	7.4 (6-9)	0.11	46.3 ±22.0	43.2 ±20.4	-	30.3 ±16.4	28.4 ±15.2	-
Diaphragmatic Descending	37.2 ±17.5	5.5 (5-6)	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 (3-4)	-
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 x s x 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 8: Aortic Stiffness Before and After exercise training, Stratified by Older (Age >37 Years) and Younger (Age ≥37 Years) participants. Values are n, median (interquartile range), mean ±SD. Only p values that are significant at 0.10 false discovery rate are reported. Z_c = characteristic impedance.

Knee assessment:

During the second year of recruitment, 115 participants entered the study. Thirty-one of our enrolled cohort failed to complete the training program and were considered 'non-marathon runners' due to reasons not directly linked to their pretraining health condition (Figure 7). Eighty-three participants completed the marathon, 71 of these attended the clinic for a second MRI scan half a month after the marathon, as did 11 of the 31 non-marathon runners who failed to complete the training and did not start the marathon. Non-marathon runners were used for comparison with the marathon runners' group.

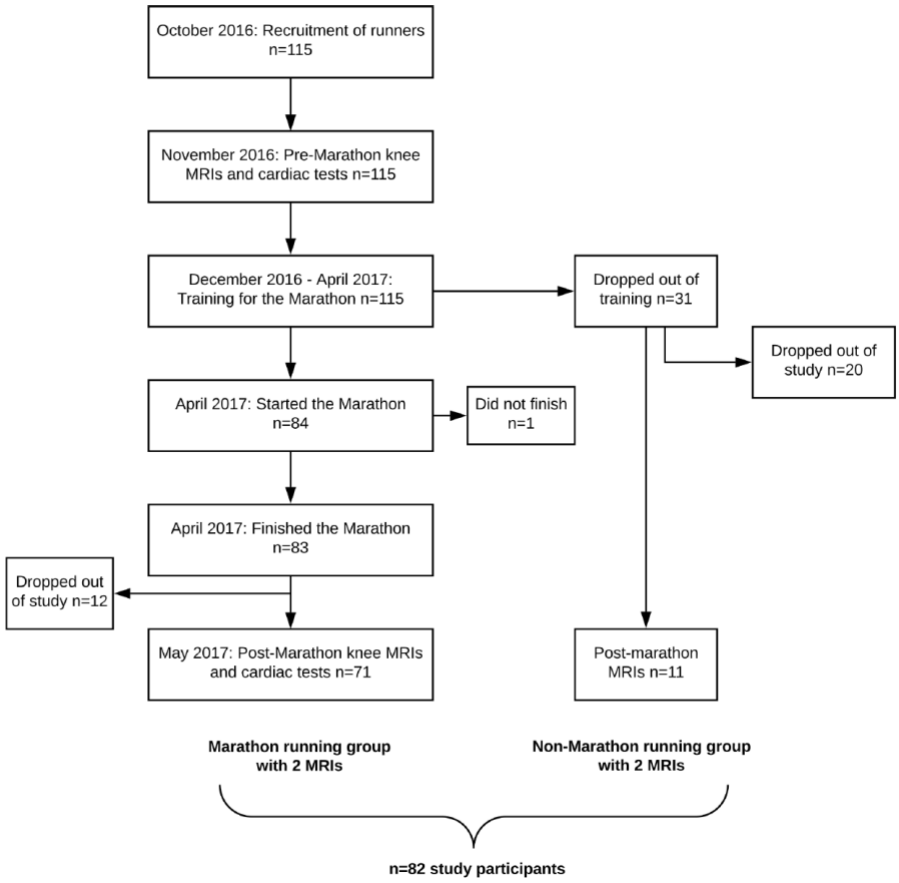

Figure 7: From Horga et al. [83] CONSORT diagram for the knee joint substudy

Seventy out of the 82 participants completed KOOS questionnaires both before and after the marathon: 65/71 marathon runners and 5/11 non-marathon runners. Both pre-marathon and post-marathon KOOS scores in marathon runners and non-marathon runners were normally distributed. No significant changes between pre-marathon and post-marathon KOOS scores were identified in runners for the individual questionnaire items related to: symptoms ($p = 0.981$), pain ($p = 0.121$), daily activity ($p = 0.303$), sports and recreational activities ($p = 0.133$), quality of life ($p = 0.096$). No significant differences between the same two scanning time points were reported among non-marathon runners: symptoms ($p = 0.375$), pain ($p = 0.250$), daily activity ($p > 0.999$), sports and recreational activities ($p > 0.999$), quality of life ($p = 0.250$). [83]

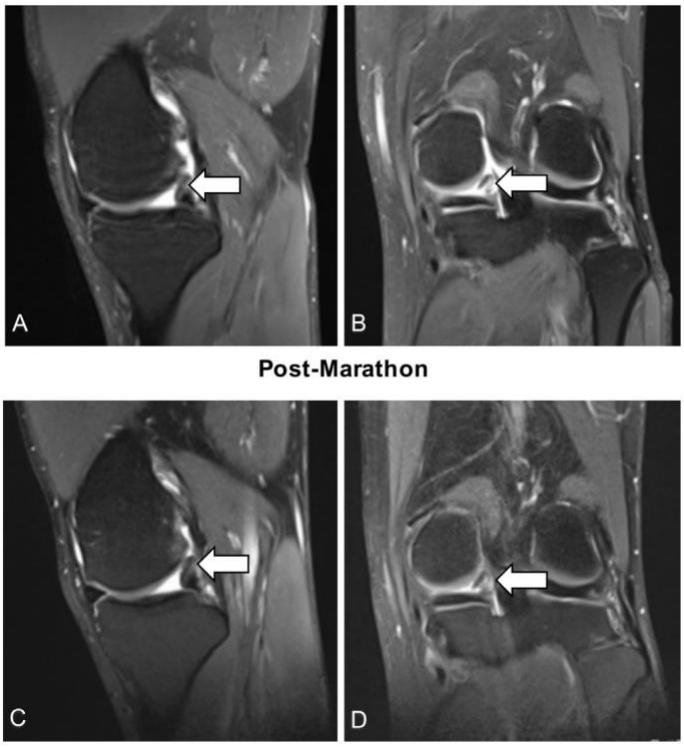

Figure 8: from Horga et al. [83] MRI scans of a 45 year old marathon runner with finishing time 3 hours and 51 min who was diagnosed during the pretraining period with bucket-handle tear of the posterior horn of the medial meniscus as it is indicated by (A) the sagittal PD FS image (TR=4670, TE=41, slice thickness: 3 mm) (white arrow) and the (B) coronal PD FS image (TR=5240, TE=41, slice thickness: 3 mm) where the meniscal flap within the intercondylar notch (arrow) is shown. The status of the meniscal tear did not change in 2 weeks after the marathon (see C, (D)). PD FS, proton density-weighted fat suppressed; TR, repetition time; TE, echo time.

Meniscus

Before the marathon, 51 (36%) of 142 knees, of those who finished the marathon, had meniscal tears (Figure 8) and 23 knees (16%) had meniscal signal hyperintensity. Figure 8. There were no significant differences in the prevalence of meniscal lesions between pre-marathon and post-marathon scans. After the marathon, only one runner showed an increased grade from a normal meniscus to horizontal tear in the left knee (Table 9; 40-year-old woman; marathon finishing time: 6 hours 20 min). Menisci of all other scanned knees remained unchanged. The majority of the meniscal lesions (83%) were seen in the posterior horn of the medial meniscus. Out of the 84 participants who entered the race, 37 were diagnosed with meniscal tears and 47 were tear-free at the pre-marathon/pre-training MRI scan.[83] Only one participant who had a meniscal tear did not finish the marathon and this participant was not included in the statistical analysis. There was no significant difference in the finishing times between the two groups (meniscal tear present/meniscal tear absent) ($p = 0.135$). In non-marathon runners, six out of 22 knees (27%) had meniscal tears and five knees (23%) presented with meniscal signal hyperintensity at the first time point of scanning. No change was seen after the marathon (Table 9).

	Marathon runners (N=142 knees)			**Non-marathon runners (N=22 knees)**		
	Number of Post-M lesions			**Number of Post-M lesions**		
Knee abnormalities per structure	**New/worsened**	**Improved**	**Significant change from Pre-M**	**New/worsened**	**Improved**	**Significant change from Pre-M**
Meniscal tears	1	0	n.s.	0	0	n.s.
Cartilage lesions	25	2	Lateral patella	4	0	n.s.
Patello-femoral	21	1	p=0.0005*	3	0	
Tibio-femoral	4	1		1	0	
BME lesions	26	23	Medial tibia	3	3	n.s.
Patello-femoral	19	2	p=0.011+	3	1	
Tibio-femoral	7	21		0	2	
Tendon lesions	13	2	Semimembranosus p=0.016*	2	0	n.s.
Ligament lesions	2	2	n.s.	0	0	n.s.
ITBFS	15	0	ITB p<0.0001*	1	1	n.s.
Prepatellar bursistis	7	0	Prepatellar bursitis p=0.016	1	0	n.s.

*Table 9: Number of postmarathon lesions in different structures before and after the marathon/training, in 142 knees of 71 marathon runners and 22 knees of 11 non-marathon runners. From Horga et al. [83] All abnormalities were recorded including Grade 1 abnormalities (all grades different from 0 were defined as 'lesions'). P values<0.05 indicate significant changes in the knees between the premarathon and postmarathon time points.See online supplementary appendices 2 and 4 for further details. *Indicate significant worsening. †Indicate significant improvement in the extent of lesion. BME, bone marrow oedema; ITBFS, iliotibial band friction syndrome; n.s., not significant; Post-M, post-marathon; Pre-M, pre-marathon.*

Articular cartilage

Before the marathon, more than half of the knees of those that went on to finish the marathon, already had cartilage damage (92 knees, 65%), with the majority of lesions located in the patellofemoral joint (70%) and all were asymptomatic. The patellofemoral joint was most affected after the marathon (21 cartilage lesions), especially the lateral patellar facet (12 lesions, p=0.0005; Table 9; Figure 9).[83] Similarly, in non-marathon runners, more than half of the knees had cartilage lesions (15 out of 22 knees, 68%) prior to training. After training, four lesions worsened (Table 9), with three of them being located in the patella.

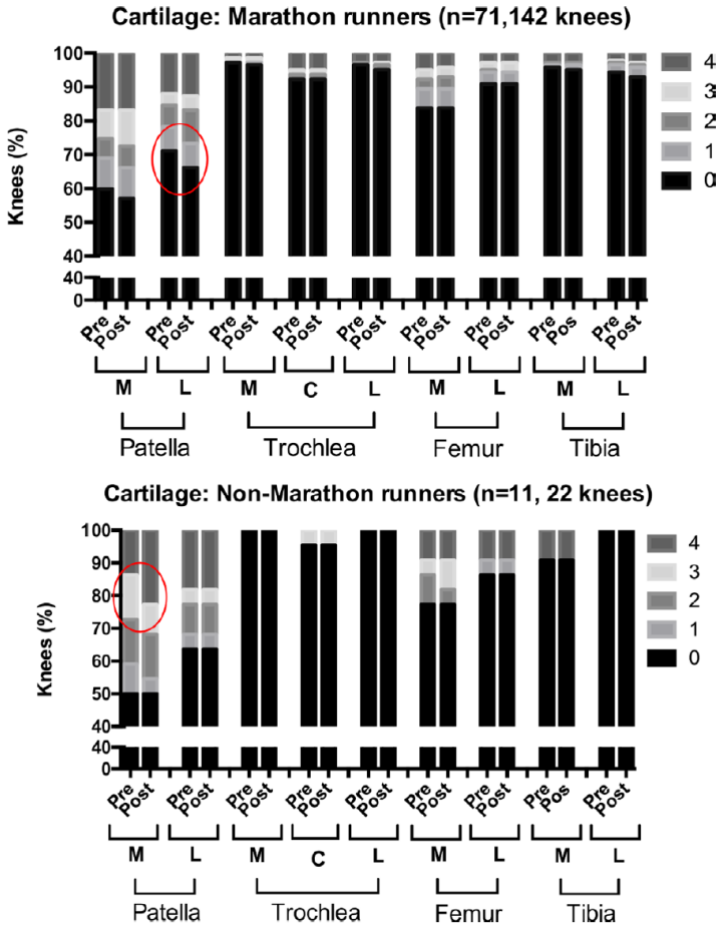

Figure 9: from Horga et al. [83] The prevalence of knees with premarathon and postmarathon cartilage lesions in marathon runners and non-marathon runners. The lesions were graded using the modified Noyes and Stabler scoring system and scores 0–4 were assigned: 1—areas of heterogeneous signal intensity on fat saturated IW FSE sequences; 2—cartilage defects that involve less than 1/2 of cartilage thickness; 3—cartilage defects that involve more than 1/2 of cartilage thickness but less than full thickness. 4—full thickness cartilage defects exposing the bone. Red circles indicate changes in the grading of lesions in the knees of participants between the premarathon and postmarathon scans. C, central; L, lateral; M, medial; IW FSE, intermediate-weighted fast spin-echo.

Discussion

These data show cardiac and vascular remodelling in healthy sedentary adults undergoing medium-term, unsupervised physical training of mild intensity. There is an age dependence, with more cardiac remodelling in younger subjects and more vascular remodelling in older subjects (Figure 11). In older, slower and male marathon runners, it was possible to reverse the consequences of ageing on vessel stiffening by approximately 4 years, as measured in the aorta rather than more peripheral vessels. Furthermore, our data show the changes in the pathology of the knee related to physical training.

Cardiovascular remodelling

As age increases peak physical performance decreases, lean mass is reduced, fat mass is increased [84],[85] and individuals are less able to train. [86] We sought to understand these changes in more detail. Here, the U35s and O35s were all first-time marathon runners, but they differ by more than just age. Although it is not possible to fully unpick the contribution of differences (baseline fitness, training schedule, commitment, age-related whole-organism responsivity to training) and the net amount of physical exercise against age in determining cardiovascular remodelling, baseline age-adjusted peak oxygen consumption and marathon completion and injury rates were not age-dependent, suggesting that baseline fitness, training schedules and commitment were not the primary cause of the remodelling differences. Moreover, performance times were not consistent with what expected after following the suggested training program (approximately 30 min slower than the average completion time for the London Marathon) but are more compatible with a mild intensity training, i.e. an exercise doses achievable in real-world novice runners. Examining the consequences of first-time marathon training helps to understand the benefits of real-world exercise behaviour 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.

Ageing is associated with impaired cardiovascular elasticity [87],[7] and reduced cardiac responsivity to sympathetic stimulation. [88] Histologically, these features correspond to 1) quantitative and qualitative changes in collagen, 2) a reduction in cardiomyocyte number with compensatory hypertrophy of the remaining cells [1] and 3) changes in cardiac innervation.[19], [20] Functionally, this translates into cardiac diastolic dysfunction and dromotropic/inotropic impairment, associated with increased afterload and leading to increased ventricular filling pressure and impaired exercise tolerance. At the same time, in healthy individuals, chronological ageing leads to a gradual increase in aortic stiffness and elevated cardiovascular risk. Combined, cardiac and vascular ageing is critical in determining exercise tolerance: in fact, the impairment in cardiac response during strenuous exercise observed in aged people [89] is entirely reversible by reducing the loading conditions. [90] 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. [91] Cross-sectional studies have shown that moderate-intensity exercise at 4 to 5 days/week preserves "youthful" compliance of the carotid artery. [92]

Here, in the O35 group, we observed an improvement in vascular function,[35] and peripheral resistance. We hypothesize that mild-intensity training may unload the myocardium and improve ventriculo-arterial coupling, thereby increasing cardiovascular efficiency meaning that stimulated cardiac growth was counteracted – an overall beneficial set of linked changes.[93]

The improvement in aortic stiffness was functional, due to blood pressure lowering, as well as intrinsic due to structural changes in the descending aorta. (Figure 10) Also, the potential role of reduced sympathetic tone must be mentioned.[94] This is supported by wave separation analysis, which showed that reflection magnitude was unchanged. One study of 13 men observed similar benefits after just 4 weeks of training,[95] but other 2- to 4-month studies observed that the reduction in stiffness was predominantly functional. [96], [97] Unlike previous studies, we used direct CMR assessment of the aorta over a longer duration of training for aortic remodelling. 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.[98] Older, male runners had a greater reduction in aortic stiffness, attributable to greater baseline BP and aortic stiffness. Although aortic stiffening increases significantly after the age of 50 years, these data suggest that this is in part modifiable in non-hypertensive individuals.[99] 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.[100] Conversely, the distal aorta media contains a higher proportion of smooth muscle that may be more readily modifiable within a 6-month period.[101] 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. [97], [102] Regional (PWV) and local (distensibility) measurement of aortic stiffness both capture this heterogeneity, but they are associated with different cardiovascular outcomes and demonstrate distinct sensitivities to downstream pathological manifestations of arterial stiffening. [37], [103] 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 haemodynamics.

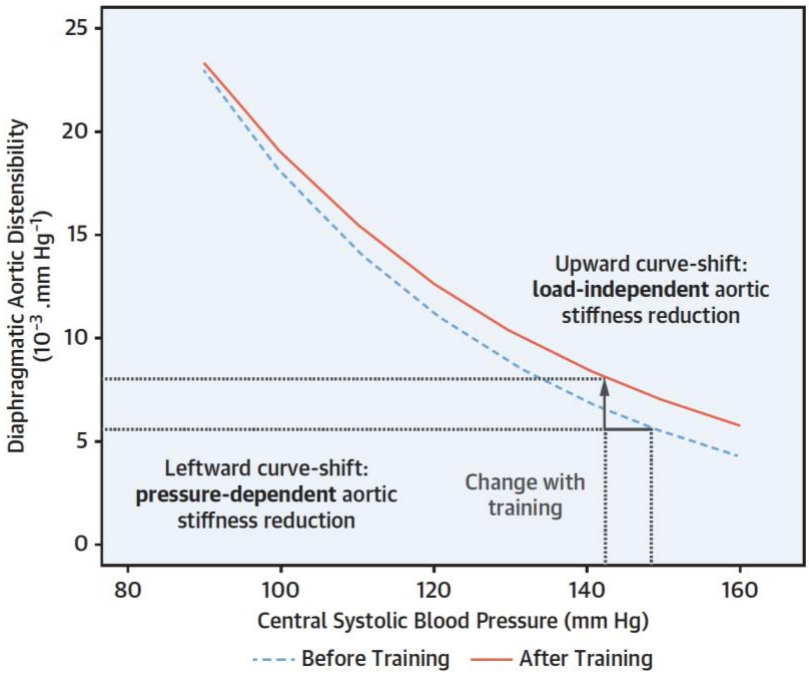

Figure 10: Reduction in Aortic Stiffness With Exercise Stiffness Is Due to Both Intrinsic Structural (Load-Independent) and Functional (Pressure-Dependent) Changes. From Bhuva et al. [62] At higher arterial pressure, the aorta is functionally stiffer, but this relationship is not linear. Exercise training results in a reduction in pressure-dependent distensibility (leftward shift along the curve), and additionally a reduction in intrinsic b-stiffness (upward shift of the curve), contributing to a greater reduction in stiffness (black arrows and lines). In this schematic, data are fitted to an exponential for the cohort both before and after exercise training.

For the U35s, possessing a greater number of smaller myocytes, an effective response to sympathetic stimulation and loading conditions already well coupled to vascular function, an increase in LV volumes along the lines expected for "athlete's heart" was seen. [104]

Finally, no changes in ECV were observed in different study conditions, arguably because the amount of exercise undertaken was insufficient to induce a measurable change in the cellular/extracellular tissue component ratio, or because any changes were proportionate with equal changes in intracellular and extracellular compartments.[105] Nevertheless, we believe that the potential significance of our results is also related to their epidemiological impact: this kind and entity of exercise is generalizable to the real-world population and is feasible outside a structured training program.

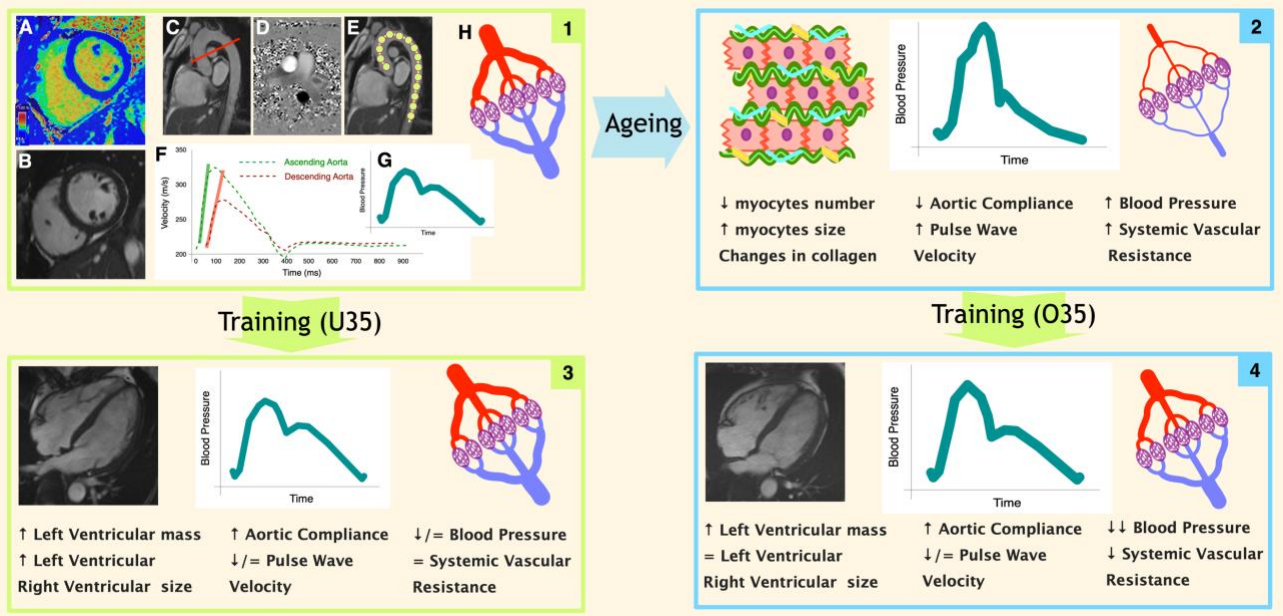

Figure 11: from Torlasco et al [78] Effects of ageing and physical training on the continuum of cardiovascular system remodelling. Panel 1: Cardiac and vascular assessment by cardiac magnetic resonance (a) extracellular volume; (b) function and mass; (c), (d) and (e) vascular function acquisitions to derive pulse wave velocity and arterial compliance by obtaining distance and high temporal resolution (g) flow and using least squares estimate of systolic upslopes (f). Graphical schematics of systemic vascular resistance (h). Panel 2: Healthy ageing is characterized by a reduction in myocyte numbers, compensatory hypertrophy and collagen alterations with vascular changes of arterial stiffening, increased pulse wave velocity, reduced arterial compliance and increased systemic vascular resistance. Physical training here induced cardiac plasticity (increase in left ventricular mass and chamber volume) in individuals under 35 years (U35), with minimal blood pressure changes (panels 1 to 3). In individuals aged 35 years and older (O35), more vascular plasticity (systemic vascular resistance drop, systemic blood pressure drops) along with mild left ventricular mass increase (panels 2 to 4) are observed.

Knee joint

Data from MRI scans of 164 knees from 82 novice, middle-aged marathon runners found damage in some areas of the knee (lateral patella cartilage and bone, the iliotibial band) and improvement in other areas (subchondral bone of the femoral and tibial condyles) as a result of training for, and running a marathon. Meniscal damage did not prevent marathon running. The improvements seen in the BME of the subchondral bone of the medial compartment may suggest that marathon running and/or training could have a protective effect on the knee joints of sedentary asymptomatic individuals.[106] Perhaps regular running prevents medial compartment overload due to muscle strengthening.[107] Further investigations are needed involving longer follow-up but the implications of these findings are important because subchondral bone marrow defects are linked with the onset of osteoarthritis,[46] and exercise is recommended for the treatment of osteoarthritis.

Our study helps to understand the optimal dose of exercise for human knee joints. Marathon training and running may be above the dose recommended for the patellofemoral joint - or recovery treatments should be targeted at this area of the knee. However, a marathon seems to be a satisfactory dose of exercise for the medial and lateral tibio-femoral joints. Before the marathon, we found a number of asymptomatic meniscal tears—including bucket-handle tears. After the marathon, the tears did not develop further, supporting conservative/non-surgical management of meniscal injuries in general, if asymptomatic.

Limitations

We acknowledge some limitations, including a potential selection bias related to the decision to run a marathon for the first time and the absence of a non-running control group. Also, age differences may reflect birth cohort bias rather than ageing with different nutrition, lifestyle and gestational conditions. There is some evidence of this with ex-smoker rates different between cohorts. The cohorts here were matched for sex, but not ethnically diverse. 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.[108] From these data, however, those with higher SBP at baseline appeared to derive greater benefit. We did not assess heart rhythm disturbances, although this is a relevant issue in athletes. This study was not designed to provide structured training, but rather to observe the effects of real-world preparation for a marathon, which randomised 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 semisupine, 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 behavioural factors), or alterations in lipid profiles and glucose metabolism, although these have not been previously associated with changes in aortic stiffness. [33] We did not examine the effect of exercise on peripheral arteries or endothelial dysfunction. Although individual participants served as internal controls, there may have been run-in bias for the initial BP measurement. This appears unlikely, as BP changes would not have been age-related nor correlated with the change in separate measures (e.g., aortic stiffness) with training. Estimated aortic ages are approximations and are 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 time point assessment.

This area warrants further study. We measured distensibility on modulus imaging acquired at 1.5-T 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.[59] If error was introduced into distensibility measurements related to through-plane motion, the resultant noise would minimize 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 ~6 mm Hg higher in the descending thoracic than the ascending aorta.[61] This PP amplification is not accounted for in our analysis, because it would have involved invasive measures of aortic pressure at each location. 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 published data for comparison. [109] Unlike Voges et al., [109] central rather than brachial PP was used, which would explain greater distensibility, and the use of 1.5-T phase-contrast modulus may accentuate image contrast differences between 3T gradient echo sequences.

About the knee MRI, reporting involves a certain level of bias but we tried to minimise it by involving two independent radiologists in the image analysis. Second, prestudy lifestyle details such as sport activities were not available and could not be accounted for; however, the participants were sedentary at recruitment and followed a standardised pre-marathon training programme. Lastly, the exact times of dropping out from training by non-marathon runners were unavailable and could not be commented on.

Future perspectives and conclusion

In conclusion, these data show differential cardiac and vascular remodelling with age in response to unsupervised exercise, a physiological stimulus reflecting a “real world” training, with remodelling being more cardiac in youth and more vascular with age.

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. [110] Our findings may have implications for cardiac rehabilitation, where vascular function and peripheral resistance changes could be tested as an efficacy endpoint. There may also be relevance to HFpEF, where a component of reversible vascular dysfunction may explain the benefits observed after physical training despite unchanged cardiac function – the idea that at least some HFpEF has a significant and reversible vascular dysfunction component is not widely considered. Additional points that need clarification are the mechanisms underlying these observations and the impact of sex on cardiovascular ageing and its interaction with physical exercise.

Finally, we question whether the lesions that appeared/worsened from pre-existing ones after the marathon resolve at a long-term follow-up. Further research is required to clarify whether the marathon damage to the knee joint structures is permanent and how serious it is.

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Supplemental Material

		Whole cohort (n=138)		U35 (≤34 years) (n=71)			O35 (≥35 years) (n=68)		p condition	p age	p interaction
BSA (m^2)	Baseline	1.9 ± 0.2		1.9 ± 0.2			1.9 ± 0.2		n.s.	n.s.	n.s.
	Follow-up	1.9 ± 0.2		1.9 ± 0.2			1.9 ± 0.2				
CMR											
LV EDV (ml)	Baseline	162 ± 35		169 ± 38			154 ± 32	§	0.159	0.001	0.008
	Follow-up	164 ± 36		174 ± 39		**	152 ± 31	§§			
LV ESV (ml)	Baseline	57 ± 17		61 ± 18			52 ± 15		0.068	0.001	0.009
	Follow-up	58 ± 16		65 ± 18		**	52 ± 14	§§			
LV SV (ml)	Baseline	105 ± 24		108 ± 25			101 ± 21		0.83	0.047	0.341
	Follow-up	105 ± 23		110 ± 25			101 ± 20	§			
RV EDV (ml)	Baseline	164 ± 41		173 ± 42			155 ± 39		0.017	0.001	0.316
	Follow-up	168 ± 40		179 ± 42		*	157 ± 33				
RV ESV (ml)	Baseline	65 ± 18		74 ± 20			55 ± 17				
	Follow-up	67 ± 20		77 ± 22			57 ± 18				
RV SV (ml)	Baseline	99 ± 21		99 ± 23			100 ± 20				
	Follow-up	101 ± 22		101 ± 24			100 ± 21				
LV mass (g)	Baseline	117 ± 32		121 ± 32			112 ± 31		<.0001	0.061	0.471
	Follow-up	121 ± 32		127 ± 32		***	116 ± 32	**			
Septal wall thickness (mm)	Baseline	6.8 ± 1.6		6.8 ± 1.7			6.8 ± 1.8		0.61	0.688	0.975
	Follow-up	6.9 ± 1.7		6.9 ± 1.7			6.9 ± 1.6				
Lateral wall thickness (mm)	Baseline	6.4 ± 2		6.7 ± 2			6.2 ± 1.8		0.678	0.258	0.514
	Follow-up	6.3 ± 1.6		6.4 ± 1.8			6.2 ± 1.6				
Native blood T1 (msec)	Baseline	1606 ± 69		1601 ± 67			1611 ± 72		0.176	0.543	0.212
	Follow-up	1600 ± 68		1602 ± 68			1598 ± 68				
Myocardial T1 post-Gd (msec)	Baseline	620 ± 46		632 ± 37			607 ± 51		0.8334	<.0001	0.47
	Follow-up	621 ± 41		635 ± 35			606 ± 42				

Blood T1 post-Gd (msec)	Baseline	503	±	61	514	±	51		491	±	68		0.431	0.001	0.291
	Follow-up	508	±	58	514	±	49		490	±	62				
Partition coefficient (Lambda)	Baseline	46	±	3	45	±	3		46	±	4	*§*	0.444	0.045	0.45
	Follow-up	46	±	3	45	±	3		46	±	4				
ECV	Baseline	27.1	±	2.5	26.9	±	2.3		27.4	±	2.6		0.006	0.002	0.1
	Follow-up	26.2	±	2.5	25.5	±	5.7	**	27.3	±	2.1				
LA volume (ml)	Baseline	69	±	20	67	±	22		70	±	18		0.788	0.615	0.026
	Follow-up	69	±	20	70	±	21		68	±	18				
CPET															
% of predicted VO2 max (%)	Baseline	108	±	17	106	±	16		113	±	18		0.204	0.146	0.371
	Follow-up	112	±	19	110	±	17		116	±	21				
Peak HR (beats/min)	Baseline	164	±	15	168	±	14		159	±	16	*§§*	0.354	<.0001	0.072
	Follow-up	165	±	15	172	±	15		158	±	15				
VE max	Baseline	95	±	29	97	±	30		92	±	28		0.001	0.21	0.922
	Follow-up	88	±	25	91	±	26	*	85	±	24	*			
Peak O2 pulse	Baseline	15.4	±	4	16	±	4		14.8	±	4		0.167	0.019	0.629
	Follow-up	15.5	±	4	16.4	±	4		14.8	±	4	*§*			
Biochemistry															
Hb (g/dl)	Baseline	14	±	13	14	±	12		14	±	14		0.004	0.88	0.148
	Follow-up	14	±	13	14	±	12		14	±	16				
Hct (%)	Baseline	42	±	4	42	±	3		42	±	4		0.002	0.174	0.003
	Follow-up	43	±	4	43	±	3	***	42	±	4				
Creatinine (mg/dl)	Baseline	0.74	±	13	0.74	±	13		0.75	±	12		0.002	0.166	0.386
	Follow-up	0.7	±	15	70	±	13		72	±	17				

*Table S 1: Baseline and post-marathon tests results for the patients who completed the study, whole sample, U35 and O35. Data are expressed as mean ±SD. * = p pre vs post <0.05; ** = p pre vs post <0.01; *** = p pre vs post <.0001; § = p U35 vs O35 <0.05; §§ = § = p U35 vs O35 <0.05; §§ = p U35 vs O35 <0.01; §§§ = p U35 vs O35 <0.001.*

BEGINNER TRAINING PLAN

BEGINNER TRAINING PLAN

This training plan is aimed at novice marathon runners covering the distance for the first time, with a few tweaks and challenges if you want to test yourself, or if you feel like pushing on a bit if your training is going really well.

The plan assumes that you will run three times a week and that you've done very little running in the past but are generally in good health and committed to your marathon journey.

The days of the week shown are not fixed and only proposed. If you change them, try to ensure that a run day is followed by a rest day (for example, run on Monday, Wednesday and Saturday or Tuesday, Thursday and Sunday).

DIFFERENT TYPES OF TRAINING RUN

EASY RUNS
(less than 60 per cent maximum effort)

During an easy run, you should feel relaxed. You should be breathing comfortably and be capable of holding a conversation throughout the run. If you're a new runner nothing may feel easy at first – slow down, walk if necessary and control your effort.

STEADY RUNS
(60-70 per cent maximum effort)

These are the bread and butter of your training, the 'miles in the bank'. Steady runs build the base that is the foundation for the rest of your training. Conversations are still possible at this pace but in sentences rather than long gossip.

TEMPO RUNS
(70-80 per cent maximum effort)

Running at tempo pace is great for improving your running economy. It's a sustained cruise pace that requires concentration. You will find these runs slightly uncomfortable as you try to run faster but they are worth it.

LONG RUNS

These are a real focus of the plan. They should be used to develop strength and endurance but also to practise your target marathon pace and control. Long runs are shown in both time and distance.

WEEK 1

MONDAY	REST DAY - Increase time on your feet and build a strong foundation and routine
TUESDAY	WALK 30 MINUTES
WEDNESDAY	REST DAY
THURSDAY	RUN/WALK 40 MINUTES - 10-minute brisk walk, 20-minute easy run, 10-minute brisk walk
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN/WALK 50 MINUTES - 10-minute walk, 30-minute easy run, 10-minute walk

WEEK 2

MONDAY	REST DAY - The first few weeks are important. Find the time to fit in your workouts
TUESDAY	RUN/WALK 40 MINUTES - (10 minute walk, 10 minute run) x 2
WEDNESDAY	REST DAY
THURSDAY	RUN/WALK 50 MINUTES - 10-minute brisk walk, 30-minute easy run, 10-minute brisk walk
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN/WALK 65 MINUTES - 10-minute walk, 20-minute easy run, 10-minute walk, 15-minute easy run, 10-minute walk

WEEK 3

MONDAY	REST DAY - You're doing a great job. The more you do the easier it feels!
TUESDAY	RUN/WALK 40 MINUTES - 5-minute walk, 30-minute easy run, 5-minute walk
WEDNESDAY	REST DAY
THURSDAY	RUN/WALK 50 MINUTES - 5-minute brisk walk, 40-minute easy run, 5-minute brisk walk
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN/WALK 80 MINUTES - 10-minute walk, 30-minute jog, 10-minute walk, 20-minute jog, 10-minute walk

WEEK 4

MONDAY	REST DAY - The first block of four weeks is almost done. Stick to your plan this week and build up to your longest time on your feet
TUESDAY	40 MINUTES EASY RUN
WEDNESDAY	REST DAY
THURSDAY	RUN/WALK 55 MINUTES - 5-minute brisk walk, 45-minute easy run, 5-minute brisk walk
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN/WALK 90 MINUTES - 10-minute walk, 30-minute jog, 10-minute walk, 30-minute jog, 10-minute walk, or distance goal of 6 to 8 miles

WEEK 5

MONDAY	REST DAY - A lighter week to allow for adaptation to the training loads
TUESDAY	20 MINUTES EASY RUN
WEDNESDAY	REST DAY
THURSDAY	30 MINUTES EASY RUN
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN 52 MINUTES - 25-minute easy run, 2-minute walk, 25-minute easy run

WEEK 6

MONDAY	REST DAY - This week is when the marathon training kicks in, building more time on your feet, and introducing some mixed paced running
TUESDAY	40 MINUTES EASY RUN
WEDNESDAY	REST DAY
THURSDAY	RUN 40 MINUTES - 10-minute easy run, (30 sec tempo running, 2 minute walk) x 8, 10 minute easy run
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN/WALK 1HR 40 MINUTES - (20-minute easy run, 5-minute brisk walk) x 4, or distance goal of 6 to 8 miles

WEEK 7

MONDAY	REST DAY - A solid week in the bank allowing training to settle and routine to continue
TUESDAY	40 MINUTES EASY RUN
WEDNESDAY	REST DAY
THURSDAY	RUN 40 MINUTES - 10-minute easy run, (45 sec tempo running, 1 minute 45 sec walk/run) x 8, 10-minute easy run
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN 1HR 45 MINUTES - (30-minute jog, 5-minute brisk walk) x 3, or distance goal of 8 miles

WEEK 8

MONDAY	REST DAY - This week, feel your heart pounding and your breathing quicken with the tempo running
TUESDAY	40 MINUTES EASY RUN
WEDNESDAY	REST DAY
THURSDAY	RUN 50 MINUTES - 10-minute easy jog, (60 sec tempo running, 2 minute walk/jog) x 10, 10-minute easy jog
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN 1HR 40 MINUTES - (25-minute jog, 5-minute brisk walk) x 4, or distance goal of 8 to 10 miles

WEEK 9

MONDAY	REST DAY - The next few weeks are all about the long run, building your capacity to run the marathon. Do not worry about covering the race distance before the event, just trust the training. Practise your hydration and fuel strategies on your long runs
TUESDAY	40 MINUTES EASY RUN
WEDNESDAY	REST DAY
THURSDAY	RUN 30 MINUTES - 10-minute easy run, (4-minute tempo run, 3-minute easy jog/walk recovery) x 4, 10-minute easy run
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN 2 HOURS - (28-minute run, 2-minute walk) x 4, or distance goal of 10 to 12 miles

WEEK 10

MONDAY	REST DAY - Race practice – enter a half marathon to familiarise yourself with Race Day routines, such as pre-race meal, race clothing and hydration strategies
TUESDAY	RUN 35 MINUTES - 10-minute easy run, (3 x 3 minutes at a tempo pace with 2 minute jog recovery), 10-minute easy run
WEDNESDAY	REST DAY
THURSDAY	30 MINUTES EASY RUN
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RACE - Race a half marathon, or run for 2 hours 15 minutes, or distance goal of 12 miles

WEEK 11

MONDAY	REST DAY - The next four weeks are about getting to know your race pace. Have a target time in minutes and work out your pace per mile.
TUESDAY	45 MINUTES EASY RUN
WEDNESDAY	REST DAY
THURSDAY	RUN 60 MINUTES - 10-minute easy run, (5-minute tempo run, 3-minute easy run/walk recovery) x 5, 10 minute easy run
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN 2HRS 30 MINUTES - (28-minute easy run, 2-minute walk) x 5, or distance goal of 14 to 16 miles. Include a few miles at target marathon pace

WEEK 12

MONDAY	REST DAY - There are just three more weeks of hard training left before the taper and you start to run less and sharpen up
TUESDAY	50 MINUTES EASY RUN
WEDNESDAY	REST DAY
THURSDAY	RUN 52 MINUTES - 10-minute easy run, (6 minute tempo run, 2 minute easy run/walk recovery) x 4, 10 minute easy run
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN 3HRS - (28-minute easy run, 2-minute walk) x 6, or distance goal of 16 to 18 miles. Include a few miles at target marathon pace

WEEK 13

MONDAY	REST DAY - Dial in to your long run this week. Focus, plan and prepare. Relax, tune in, and tick off the miles
TUESDAY	50 MINUTES EASY RUN
WEDNESDAY	REST DAY
THURSDAY	RUN 50 MINUTES - 10-minute easy run, 10-minute steady run, 10 minutes at target marathon pace, 10-minute tempo run, 10-minute easy run
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN 3HRS 30 MINUTES - (28-minute easy run, 2-minute walk) x 7, or distance goal of 18 to 20 miles. Include a few miles at target marathon pace. Remember, people run at different paces so the distance covered will vary

WEEK 14

MONDAY	REST DAY - The long run is reducing in volume. Don't be tempted to do more or you will risk being tired on the Start Line
TUESDAY	40 MINUTES EASY RUN
WEDNESDAY	REST DAY
THURSDAY	RUN 50 MINUTES - 10-minute easy run, (3 minutes at target marathon pace, 3 mins faster) x 5, 10-minute easy run
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RUN 1HR 34 MINUTES - (45 minute easy run, 2 minute walk) x 2

WEEK 15

MONDAY	REST DAY - The taper is here. Doing less is all about recovering from the hard training so you can stand on the Start Line ready to do your best
TUESDAY	RUN 30 MINUTES - 30 minute easy run
WEDNESDAY	REST DAY
THURSDAY	RUN 50 MINUTES - 10-minute easy run, 20 minutes at target marathon pace, 10 minutes faster, 10-minute easy run x 8, 10-minute easy run
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	70 MINUTES EASY RUN

WEEK 16

MONDAY	REST DAY - You can only do too much this week. Relax, look back at your training and see how far you have come. You are ready!
TUESDAY	30 MINUTES EASY RUN
WEDNESDAY	REST DAY
THURSDAY	RUN 22 MINUTES - 5-minute easy run, 12 minutes at target marathon pace, 5-minute easy run
FRIDAY	REST DAY
SATURDAY	REST DAY
SUNDAY	RACE DAY - Start sensibly at your race pace, and stick to your race plan. Trust the training, smile and enjoy yourself. You can do it!

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Age matters: differences in exercise-induced cardiovascular remodelling in young and middle aged healthy sedentary individuals

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Abstract

Aims: Remodelling of the cardiovascular system (including heart and vasculature) is a dynamic process influenced by multiple physiological and pathological factors. We sought to understand whether remodelling in response to a stimulus, exercise training, altered with healthy ageing.

Methods: A total of 237 untrained healthy male and female subjects volunteering for their first time marathon were recruited. At baseline and after 6 months of unsupervised training, race completers underwent tests including 1.5T cardiac magnetic resonance, brachial and non-invasive central blood pressure assessment. For analysis, runners were divided by age into under or over 35 years (U35, O35).

Results: Injury and completion rates were similar among the groups; 138 runners (U35: $n = 71$, women 49%; O35: $n = 67$, women 51%) completed the race. On average, U35 were faster by 37 minutes (12%). Training induced a small increase in left ventricular mass in both groups (3 g/m^2, $P < 0.001$), but U35 also increased ventricular cavity sizes (left ventricular end-diastolic volume (EDV)i +3%; left ventricular end-systolic volume (ESV)i +8%; right ventricular end-diastolic volume (EDV)i +4%; right ventricular end-systolic volume (ESV)i +5%; $P < 0.01$ for all). Systemic aortic compliance fell in the whole sample by 7% ($P = 0.020$) and, especially in O35, also systemic vascular resistance (–4% in the whole sample, $P = 0.04$) and blood pressure (systolic/diastolic, whole sample: brachial –4/–3 mmHg, central –4/–2 mmHg, all $P < 0.001$; O35: brachial –6/–3 mmHg, central –6/–4 mmHg, all $P < 0.001$).

Conclusion: Medium-term, unsupervised physical training in healthy sedentary individuals induces measurable remodelling of both heart and vasculature. This amount is age dependent, with predominant cardiac remodelling when younger and predominantly vascular remodelling when older.

Keywords

Physical training, cardiac remodelling, vascular remodelling, healthy ageing

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Introduction

'Cardiac plasticity' is the ability of the myocardium to undergo reversible structural and functional changes via 'remodelling', a process that appears evolved to optimise performance.[1] It starts at the molecular level and leads to changes in myocytes, but also affects the extracellular compartments,[2–6] translating into changes in wall thickness, chambers volumes and ventricular function which can, in some cases, double the size of the heart.[1] Similar plasticity is found in the vascular tree where macroscopically measurable changes in large vessels occur, including intima-media thickness, media-to-lumen ratio and elastic properties.[7]

The overall cardiovascular phenotype at any given time is determined by age, sex, environmental factors (for example sedentary vs. athletic), disease and genetics.[8–11] Our knowledge of their relative contributions is incomplete. Ageing-related cardiac changes include a reduction in myocyte numbers (30% fall from second to seventh decade)[2,3] with hypertrophy of remaining cells in addition to alterations in contractile proteins and collagen, leading to a stiffer heart.[6,12] Vascular changes include reduced capillary density, altered collagen and elastin, and an increase in vascular stiffness, with increased peripheral resistance.[7] The two compartments interact directly via vascular coupling (volume and pressure loading) and through paracrine and neurohumoral control.[13,14]

These changes may be reversible and plastic, but current knowledge is incomplete. Physiological exercise can explore the system: intense physical exercise leads to the 'athlete's heart', while moderate training has been associated with increased capillarity, enlargement of conduit vessels[15] and a delayed age-related increase in cardiac stiffening.[16]

Society is currently changing with: (a) demographic ageing, with 22% of people expected to be over 65 years of age by 2040;[17] (b) activity changes, that is, increasingly sedentary lifestyles for some and increasing recreational running in others;[18] (c) altering emergent disease profiles, for example, heart failure with preserved ejection fraction (HFpEF).[19] Accordingly, we wished to explore the relationship between healthy ageing and differences in cardiovascular adaptation in response to a stimulus, here moderate, unsupervised, medium-term aerobic exercise.

Methods

This was a prospective observational study, evaluating first-time marathon runners of both sexes, unaware of pre-existing cardiovascular conditions and not on medications, sedentary. Exclusion criteria included cardiovascular disease uncovered during preliminary investigations and contraindication to cardiac magnetic resonance (CMR). The study was advertised by email over two consecutive years to novice marathon runners, identified through the database records of the Virgin Money London Marathon, and on social media. Interested runners contacted a dedicated call centre and were given an appointment for eligibility assessment and recruitment.

The study protocol has already been described.[20–23] Briefly, it included:

- Cardiopulmonary exercise test (CPET) using a semi-recumbent tilting cycle ergometer (Schiller ERG 911 BP/LS; Schiller, Switzerland) and a dedicated metabolic cart (Quark CPET; COSMED, Rome, Italy)[24]
- Allometry and bioimpedance (BC-418; Tanita, USA)
- CMR (1.5T Aera; Siemens Medical Solution, Erlangen, Germany), performed accordingly to international guidelines,[25] including parametric T1 mapping and extracellular volume (ECV), pulse wave velocity (PWV) measured with phase-contrast magnetic resonance imaging (MRI) and late gadolinium enhancement (LGE) images.[26] Image analysis was performed by three experienced operators. See Supplementary Table 2 for intra and inter-operator reproducibility data.
- Brachial and non-invasive central- blood pressure (BP) assessment and wave analysis using a Cardioscope II BP+ device (USCOM, Sydney, NSW, Australia)[27]
- Haematocrit and serum creatinine.

Systemic vascular resistance and systemic aortic compliance were also calculated as follows:

$$\mathrm{SVR} = \frac{\mathrm{MAP}}{\mathrm{CO}} * 80$$

$$\mathrm{SAC} = \frac{\mathrm{SV}}{\mathrm{SBP} - \mathrm{DBP}}$$

where SVR is systemic vascular resistance; MAP is mean arterial pressure; CO is cardiac output; SAC is systemic arterial compliance, SV is stroke volume; SBP is systolic blood pressure; DBP is diastolic blood pressure.

All measurements were carried out before training started, 6 months before the marathon, and repeated between one and 3weeks after the race, to avoid the acute effects of the race. It was recommended that participants followed the race organisers' 'Beginner's training plan' (see Appendix 1), but alternative training plans were allowed. The calculation of synthetic ECV[28]

was preferred because haematocrit, needed in order to calculate normal ECV, was unavailable at follow-up in 35 subjects due to the cyberattack that affected NHS and the hospital laboratory immediately before the study dates.

All procedures were in accordance with the principles of the Declaration of Helsinki, all participants gave written informed consent, and the study was approved by the London–Queen Square National Research Ethics Service Committee (15/LO/0086).

Statistical analysis

Quantitative variables are expressed as mean ± standard deviation (SD) or (range) and categorical variables as an absolute number with percentage in parentheses. Only the subjects who completed the study were included in the analysis. To assess the cardiovascular effects of aerobic exercises in different age groups, we used linear mixed-effects models accounting for repeated measurements with an unstructured covariance matrix, fitting the models by maximising the restricted log-likelihood followed by a posteriori contrasts when applicable. The false discovery rate algorithm was used for multiple post-hoc comparisons. The variables were transformed to handle possible violations of the hypothesis of normality of the residuals. For analysis of the age effect, we split recruited runners into two groups, under 35 (U35) and over 35 (O35), when a runner is less than 35 or 35 years or older, respectively, accordingly to the classification of 'young' versus 'master' athlete. Linear regression analysis was also performed (results in Appendix 2). A α level of 0.05 was used for all hypothesis tests; analyses were performed using R Core Team software (2018), Vienna, Austria.

Results

Study population

Two hundred and thirty-seven runners were recruited. Among them 166 (70%) completed the race, 52 (22%) interrupted their training following musculoskeletal injury, 19 (8%) did not compete for other reasons. Among the race completers, 27 did not attend for follow-up, one was excluded after being diagnosed with hypertension. The final cohort consisted of 138 subjects who underwent evaluations at 180 ± 10 days before the London Marathon and 16 ± 8 days after (Figure 1). The baseline mean age was 37 ± 10 years (range 21–69), 51% were women (mean age 37 ± 10 years, 47% < 35 years), 49% were men (mean age 37 ± 11 years, 54% < 35 years). The reported median hours of training per week were 1.9.

Baseline characteristics

We did not find any significant difference in the baseline characteristics between the subjects who completed the study or dropped out. Race finishers were similar in age and gender (U35: $n = 71$, mean age 29 ± 4 years, women 49%; O35: $n = 67$, mean age 46 ± 7 years, women 51%). The prevalence of former smokers was lower in U35 than in O35 (10% vs. 32%, respectively, $P = 0.002$). No differences were observed for ethnicity and blood tests results. See Tables 1 and 2.

The marathon completion rate and injury rate during training did not differ between age groups (Figure 1). The mean race time (hours:minutes) was 4:44 (range: 2:57–7:57) in the whole cohort. U35 were faster (mean race time in U35: 4:38 (range 2:56–6:51) against 5:15 (range 3:27–7:57) in O35).

All participants achieved a respiratory exchange ratio (RER) of 1.1 or greater at the baseline CPET. Age predicted peak oxygen uptake was 109 ± 17%, without significant differences between groups, although absolute physical performance was superior in U35 than in O35 for peak oxygen uptake (+5.6 ml/kg/min, $P < 0.001$), maximal reached power (+13 W, $P = 0.012$) and exercise time (+166 seconds, $P < 0.001$).

Mean height, weight, body surface area (BSA) did not differ between groups. On average, body mass index (BMI) was high to normal (24.4, range 16.7–35.2), and lower in U35 than O35 (U35: 23.6 ± 0.3; O35: 25.1 ± 0.4, $P = 0.009$).

Average biventricular chamber size and left ventricular (LV) mass indexed for BSA were normal in the whole sample.[29] All volumes and masses were higher in U35 than in O35 (LV end-diastolic volume (EDV)i: +8 ml/m^2; LV end-systolic volume (ESV)i: +5 ml/m^2, RV EDVi and ESVi: +10 ml/m^2; LV mass +6 g/m^2; $P < 0.001$ for all). Native T1 values and synthetic ECV were within the normal range and not different between groups.[26] There was basal infero-lateral mid-myocardial non-ischaemic LGE in one male subject in O35, both before and after training (unchanged).

Average BP was normal in the whole sample, but lower in U35 than in O35 by 5/3 mmHg for brachial SBP/DBP ($P = 0.02/0.03$, respectively) and by 6/3 mmHg for central SBP/DBP ($P = 0.004$ for central SBP and $P = 0.03$ for central DBP). Arterial PWV in the whole aorta was 6 ± 15 m/s, lower in U35 than O35 by 1.4 m/s ($P < 0.001$).[20] Similarly, SVR was on average 1135 dyn · s/cm^5, significantly lower in U35 than in O35 by 173 dyn·s/cm^5 ($P < 0.001$). Finally, SAC of the whole sample was 3.0 ± 8 ml/m^2, higher in U35 than in O35 (+0.3 ml/m^2, $P = 0.001$).

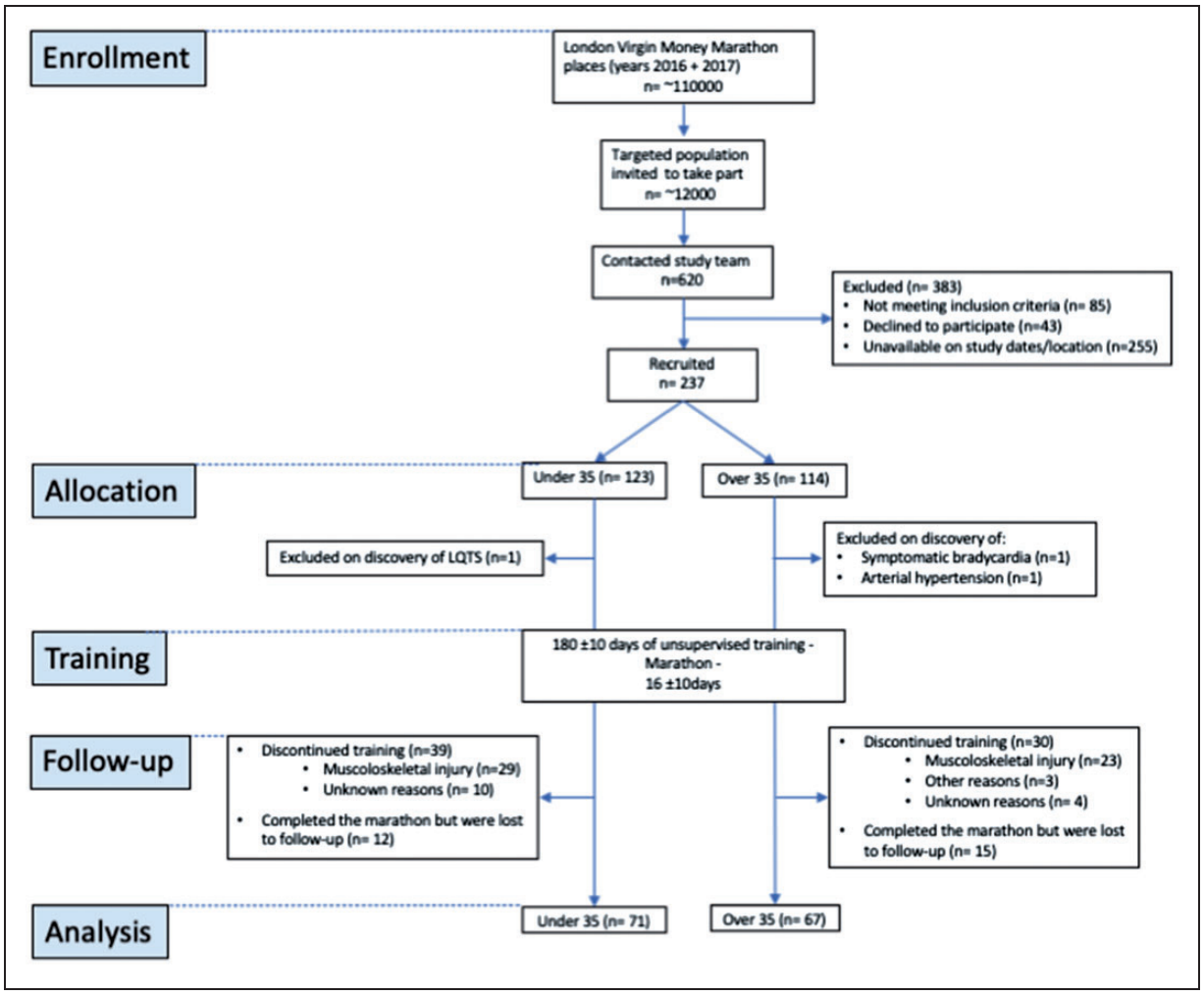

Figure 1. Consort flow diagram illustrating subject recruitment and follow up.
LQTS: long QT syndrome; U35: under 35, less than 35 years; O35: over 35, 35 years and older.

Table 1. Baseline characteristics of study participants in the final cohort, stratified by age category.

	Whole cohort		U35 (≤34 years)		O35 (≥35 years)	
n	138		71		67	
Age (years)	37	(21–69)	29	±4	46	±7
Women	70	(51%)	34	(49%)	36	(51%)
Men	68	(49%)	37	(54%)	31	(46%)
Ethnicity						
White	125	(91%)	62	(93%)	63	(89%)
Asian	4	(4%)	1	(1%)	3	(4%)
Black	3	(2%)	2	(2%)	1	(1%)
Mixed	4	(3%)	0		4	(5%)
Other	2	(1%)	0		2	(2%)
Smoking						
Non-smoker	102	(74%)	60	(85%)	42	(63%)
Current smoker	7	(5%)	4	(5bhuva%)	3	(5%)
Ex-smoker	29	(21%)	7	(10%)	22	(32%)
Exercise/week (hours)	1.9	(0–10)	1.8	(0–4)	2	(0–10)
Running time (hours:mins)	4:44	(2:57–7:57)	4:38	(2:56–6:51)	5:15	(3:27–7:57)

Data are expressed as mean (range), mean ± SD or number (%).

Table 2. Baseline and post-marathon tests results for the patients who completed the study, whole sample, U35 and O35.

Allometry	Timepoint	Whole cohort ($n = 138$)	U35 ($\leq$34 years) ($n = 71$)	O35 ($\geq$35 years) ($n = 67$)	*P* condition	*P* age	*P* interaction
Height (cm)	Baseline	172.9 ± 9.5	174.3 ± 9.5	171.6 ± 9.4	0.001	0.09	0.8
	Follow-up	172.4 ± 9.5	173.7 ± 9.5*	171.0 ± 9.5**			
Weight (kg)	Baseline	73.2 ± 13	71.8 ± 12	74.5 ± 15	0.001	0.1	0.04
	Follow-up	72.3 ± 12	71.4 ± 10	73.1 ± 14**			
BMI (kg/m^2)	Baseline	24.4 ± 0.3	23.6 ± 0.3	25.1 ± 0.4§§	0.1	0.009	0.08
	Follow-up	24.2 ± 0.3	23.6 ± 0.3	24.8 ± 0.4§			
Body fat (%)	Baseline	25 ± 8	23 ± 8	27 ± 8	0.006	0.021	0.06
	Follow-up	24 ± 9	23 ± 9	26 ± 9			
Blood pressure							
Heart rate (bpm)	Baseline	70 ± 13	71 ± 13	69 ± 13	0.3	0.9	0.4
	Follow-up	68 ± 12	68 ± 12	68 ± 13			
Brachial SBP (mmHg)	Baseline	121 ± 14	119 ± 11	124 ± 15§§	<.001	0.026	0.049
	Follow-up	117 ± 13	116 ± 10*	118 ± 15***			
Brachial DBP (mmHg)	Baseline	75 ± 7	73 ± 5	76 ± 8§§	<.001	0.020	0.028
	Follow-up	72 ± 7	72 ± 5	73 ± 8***			
Central SBP (mmHg)	Baseline	112 ± 13	109 ± 11	115 ± 14§§	<.001	0.004	0.043
	Follow-up	108 ± 13	106 ± 10	109 ± 15***			
Central DBP (mmHg)	Baseline	76 ± 7	75 ± 5	78 ± 8§§	<.001	0.030	0.011
	Follow-up	74 ± 7	73 ± 5*	74 ± 8***			
Central MAP (mmHg)	Baseline	87 ± 8	86 ± 7	91 ± 10§§	<.001	0.009	0.016
	Follow-up	85 ± 10	84 ± 7*	86 ± 10***			
Pulse wave analysis							
PWV Arch (m/s)	Baseline	4.7 ± 1.4	3.9 ± 0.6	5.6 ± 1.6§§§	0.2	<.001	0.4
	Follow-up	4.6 ± 1.2	3.9 ± 0.6	5.3 ± 1.3			
PWV descending aorta (m/s)	Baseline	8.3 ± 2.5	8.2 ± 2.6	8.5 ± 2.3	0.1	0.060	0.9
	Follow-up	7.9 ± 2.4	7.6 ± 4.9	8.2 ± 2.5			
PWV whole aorta (m/s)	Baseline	6.0 ± 1.5	5.3 ± 1	6.7 ± 1.7§§§	0.038	<.001	0.8
	Follow-up	5.7 ± 1.4	5.1 ± 0.7	6.5 ± 1.7			
SAC (ml/m^2)	Baseline	3.0 ± 0.8	3.2 ± 0.7	2.9 ± 0.9§§	0.022	0.001	>0.9
	Follow-up	3.2 ± 0.7	3.4 ± 0.7	3 ± 0.7§§			
SVR (dyn·s/cm^5)	Baseline	1135 ± 262	1052 ± 239	1225 ± 275	0.034	0.001	0.5
	Follow-up	1092 ± 246	1029 ± 255	1160 ± 239			
CMR							
LV EDVi (ml/m^2)	Baseline	86 ± 14	90 ± 14	82 ± 13§§	0.014	<.001	0.027
	Follow-up	88 ± 14	93 ± 15**	82 ± 13§§§			
LV ESVi (ml/m^2)	Baseline	30 ± 7	33 ± 8	28 ± 6§§	0.019	<.001	0.023
	Follow-up	31 ± 8	35 ± 8**	28 ± 7§§§			
SVi (ml/m^2)	Baseline	56 ± 10	58 ± 10	54 ± 9§	0.4	0.008	0.5
	Follow-up	57 ± 9	59 ± 10	54 ± 8			
LVEF (%)	Baseline	0.65 ± 0.05	0.64 ± 0.05	0.66 ± 0.05§	0.4	0.001	0.254
	Follow-up	0.64 ± 0.05	0.63 ± 0.05	0.66 ± 0.05			
CO (l/min)	Baseline	6.7 ± 1.6	7.1 ± 1.7	6.3 ± 1.5§	0.2	0.003	0.8
	Follow-up	6.6 ± 1.7	7 ± 1.8	6.1 ± 1.5			
LV mass i (g/m^2)	Baseline	62 ± 12	65 ± 12	59 ± 12	<.001	<.001	0.8
	Follow-up	65 ± 13	68 ± 12***	62 ± 13***			
LV mass/volume ratio	Baseline	0.72 ± 0.1	0.71 ± 0.1	0.73 ± 0.1	0.001	0.049	0.06
	Follow-up	0.74 ± 0.1	0.73 ± 0.1	0.76 ± 0.1**			
RV EDVi (ml/m^2)	Baseline	88 ± 15	92 ± 15	82 ± 13	0.001	<.001	0.6
	Follow-up	90 ± 16	96 ± 17**	85 ± 14			
RV ESVi (ml/m^2)	Baseline	35 ± 10	39 ± 9	29 ± 8	0.001	<.001	0.7
	Follow-up	36 ± 11	41 ± 10**	31 ± 9			
RV SVi (ml/m^2)	Baseline	53 ± 9	53 ± 10	53 ± 9	0.08	0.9	0.6
	Follow-up	54 ± 9	55 ± 9	54 ± 8			

(continued)

Table 2. Continued.

Allometry	Timepoint	Whole cohort ($n=138$)	U35 ($\leq$34 years) ($n=71$)	O35 ($\geq$35 years) ($n=67$)	*P* condition	*P* age	*P* interaction
RVEF (%)	Baseline	0.61 ± 0.06	0.58 ± 0.05	0.65 ± 0.07§§§	0.4	<.001	0.7
	Follow-up	0.61 ± 0.05	0.57 ± 0.05	0.64 ± 0.07			
LA volume i (ml/m^2)	Baseline	51 ± 29	51 ± 28	50 ± 31	0.9	0.8	0.09
	Follow-up	5029	48 ± 26	52 ± 31			
Native myocardial T1 (ms)	Baseline	1009 ± 29	1009 ± 28	1009 ± 28	0.3	0.4	0.8
	Follow-up	1006 ± 33	1006 ± 33	1006 ± 33			
Synthetic ECV (%)	Baseline	26.3 ± 3	25.8 ± 3	26.7 ± 3	0.8	0.1	0.2
	Follow-up	26.3 ± 3	26 ± 3	26.6 ± 3			
CPET							
Exercise time (s)	Baseline	674 ± 133	594 ± 104	760 ± 104	0.01	<.001	0.037
	Follow-up	695 ± 127	630 ± 115**	764 ± 100			
Peak VO_2 (ml/kg/min)	Baseline	34.5 ± 7.5	37.1 ± 6.8	31.4 ± 7	0.035	<.001	0.3
	Follow-up	35.6 ± 8.3	38.5 ± 8*	31.9 ± 7			
Peak power (W)	Baseline	216 ± 57	222 ± 54	209 ± 59	0.002	0.012	0.001
	Follow-up	220 ± 60	232 ± 59**	208 ± 60			
% of VO_2 max	Baseline	109 ± 17	106 ± 16	113 ± 18	0.2	0.1	0.4
	Follow-up	113 ± 19	110 ± 17	116 ± 21			
Peak HR (bpm)	Baseline	163 ± 15	168 ± 14	159 ± 16	0.8	<.001	0.07
	Follow-up	165 ± 15	173 ± 15	158 ± 14			
RQ	Baseline	1.22 ± 0.09	1.20 ± 0.09	1.24 ± 0.08*	0.02	0.01	0.51
	Follow-up	1.21 ± 0.08	1.19 ± 0.10	1.21 ± 0.07			

Data are expressed as mean $\pm$ SD.

*P pre vs. post <0.05; **P pre vs. post <0.01; ***P pre vs. post <0.001; §P U35 vs. O35 <0.05; §§P U35 vs. O35 <0.01; §§§P U35 vs. O35 <0.001.

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; PWV: pulse wave velocity; SAC: systemic arterial compliance; SVR: systemic vascular resistance; LV: left ventricle; EDV: end-diastolic volume; ESV: end-systolic volume; SV: stroke volume; EF: ejection fraction; CO: cardiac output; RV: right ventricle; LA: left atrium; ECV: extracellular volume.

Follow-up

Cardiopulmonary exercise testing. After training, there were small increases in overall fitness. A mild improvement was observed in peak oxygen uptake (+1 ml/kg/min, $P=0.035$). Exercise time increased on average by 21 seconds ($P=0.010$) and peak power by 4 W ($P=0.002$). Subgroup analysis showed these changes in the U35 only (exercise time +6%, peak power +5%, peak oxygen consumption (VO_2) +3%; $P<0.01$, $P<0.01$ and $P<0.05$, respectively). Resting heart rate was unchanged at follow-up.

Allometry. After training, weight fell by 900 g ($P=0.001$) and body fat by 1% ($P=0.006$) driven by O35 (on average –2%, $P<0.001$). Height decreased by 6 mm in both groups (see Table 2).

Cardiac remodelling. After training, biventricular volumes increased by an average of 2 ml/m^2 (EDVi) and 1 ml/m^2 (ESVi) ($P<0.05$ for both). At post hoc analysis, the chamber size increase was observed only in U35 (LVEDVi: +3%, LVESVi: +8%, RVEDVi: +4%, RVESVi: +5%; $P<0.001$ for all), while no change was observed in O35. A similar 4% (~3 g/m^2) increase in LV mass was observed in both groups ($P<0.001$) representing mild concentric remodelling (LV mass/volume ratio increase of 0.2), driven by O35, in whom the LV mass/volume ratio went from 0.73 ± 0.1 to 0.76 ± 0.1 ($P=0.001$).

Synthetic ECV and native myocardial T1 mapping were unchanged after training. No changes were observed in the myocardial partition coefficient, post-contrast T1 myocardial, full blood count or kidney function in either group.

Systemic haemodynamics and vascular remodelling. There was a mean 4% decrease in SVR after training ($P=0.04$), driven by O35 (baseline vs. follow-up in U35: $P=0.31$; O35: $P=0.060$;), associated with a 7% reduction in SAC ($P=0.020$), similar in U35 and O35 (baseline vs. follow-up $P=0.002$ for both) and a mild reduction in the PWV of the whole aorta ($P=0.040$), without differences between age groups. Training reduced BP, with the largest falls observed in O35. Brachial SBP/DBP dropped by 3/1 mmHg in U35 ($P=0.030$ for SBP, $P=0.08$ for DBP) and by 6/3 mmHg in O35 ($P<0.001$ for both SBP and DBP); central SBP/DBP dropped by 3/2 mmHg in U35 ($P=0.05$

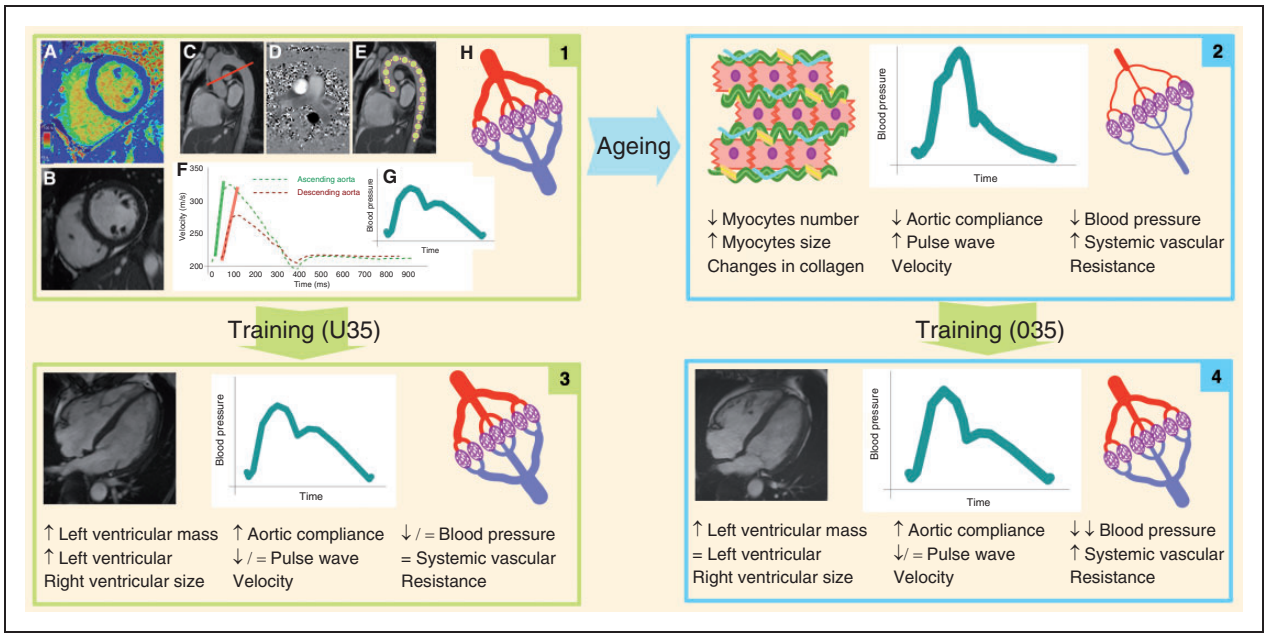

Figure 2. Effects of ageing and physical training on the continuum of cardiovascular system remodelling. Panel 1: Cardiac and vascular assessment by cardiac magnetic resonance (a) extracellular volume; (b) function and mass; (c), (d) and (e) vascular function acquisitions to derive pulse wave velocity and arterial compliance by obtaining distance and high temporal resolution (g) flow and using least squares estimate of systolic upslopes (f). Graphical schematics of systemic vascular resistance (h). Panel 2: Healthy ageing is characterised by a reduction in myocyte numbers, compensatory hypertrophy and collagen alterations with vascular changes of arterial stiffening, increased pulse wave velocity, reduced arterial compliance and increased systemic vascular resistance. Physical training here induced cardiac plasticity (increase in left ventricular mass and chamber volume) in individuals under 35 years (U35), with minimal blood pressure changes (panels 1 to 3). In individuals aged 35 years and older (O35), more vascular plasticity (systemic vascular resistance drop, systemic blood pressure drops) along with mild left ventricular mass increase (panels 2 to 4) are observed.

for SBP, $P = 0.004$ for DBP) and dropped by 6/4 mmHg in O35 ($P < 0.001$ for both SBP and DBP).

Discussion

This study explored the cardiac and vascular remodelling occurring in healthy sedentary adults of different age groups undergoing medium-term, unsupervised physical training of mild intensity. Our main findings were a more pronounced cardiac remodelling observed in younger subjects and more vascular changes, associated with early cardiac remodelling features, in older subjects (Figure 2). In particular, U35 showed an increase in ventricular LV size consistent with 6 months of endurance training in a similar age group,[30] associated with an increase in LV mass consistent with a light training schedule and a very mild reduction in BP. On the other hand, in O35s only early cardiac remodelling was noted (i.e. a LV mass increase similar to O35 but no measurable cavity dilation), associated with a more marked reduction in BP and SVR, corresponding to the effect of a low-dose BP-lowering drug on BP and to an overall reduction in vascular age of approximately 4 years.[20,21,31]

Ageing is associated with impaired cardiovascular elasticity,[7,32] and reduced cardiac responsivity to sympathetic stimulation.[33] Histologically, these features correspond to: (a) quantitative and qualitative changes in collagen; (b) a reduction in cardiomyocyte number with compensatory hypertrophy of the remaining cells;[1] and (c) changes in cardiac innervation.[6,12] Functionally, this translates into cardiac diastolic dysfunction and dromotropic/inotropic impairment, associated with increased afterload and leading to increased ventricular filling pressure and impaired exercise tolerance. Combined, cardiac and vascular ageing is critical in determining exercise tolerance; in fact, the impairment in cardiac response during strenuous exercise observed in aged people[34] is entirely reversible by reducing the loading conditions.[35]

On the other hand, endurance training is known to increase stroke volume, improve endothelial function and coronary perfusion, decrease peripheral resistance, lower BP and induce cardiac and skeletal muscle cell remodelling.[15,32,36]

Here, in the O35 group, we observed an improvement in vascular function, and peripheral resistance, consistent with previous observations.[37] We hypothesise that mild-intensity training may unload the

myocardium and improve ventriculo-arterial coupling, thereby increasing cardiovascular efficiency, meaning that stimulated cardiac growth was counteracted – an overall beneficial set of linked changes.[38]

For U35s, possessing a greater number of smaller myocytes, an effective response to sympathetic stimulation and loading conditions already well coupled to vascular function, a mild increase in LV volumes along the lines expected for 'athlete's heart' was seen.[39,40]

Finally, no changes in ECV were observed in different study conditions, arguably because any changes were proportionate with equal changes in intracellular and extracellular compartments or because the amount of exercise undertaken was insufficient to induce a measurable change in the cellular/extracellular tissue component ratio.[41]

We acknowledge a number of limitations, including the lack of a non-running control group, a potential selection bias related to the availability to take part in a research study and the lack of ethnic diversity. Here, U35s and O35s were all first-time marathon runners, but they differ by more than just age. Although it is not possible to unravel fully the contribution of differences (birth cohort bias with different nutrition, gestational conditions and lifestyle, as suggested by ex-smoker rates different between cohorts; baseline fitness; training schedule; commitment; age-related whole-organism responsivity to training) and the net amount of physical exercise against age in determining cardiovascular remodelling, baseline age-adjusted peak oxygen consumption and marathon completion and injury rates were not age dependent, suggesting that baseline fitness, training schedules and commitment were not the primary cause of the remodelling differences. Actual physical activity during the training period is unknown due to an excessive amount of missing data, but average completion times exceed those reported in age-matched wide cohorts (including professional athletes) by ~40 minutes in U35 and by ~70 minutes in O35,[18] suggesting that training intensity was mild. Exercise-induced cardiovascular remodelling is dose-dependent, with mass increase observed earlier than volume increase.[30] The mild amount of cardiovascular remodelling observed is proportional to the entity of training undertaken, and more marked changes would have been unexpected. We believe that the potential significance of our results is also related to their epidemiological impact: this kind and entity of exercise is generalisable to the real-world population and is feasible outside a structured training programme.

Finally, the study had a high drop-out rate (42%), mostly due to musculoskeletal injury (71% of total drop-out). We did not find any differences between study completers and non-completers at baseline examination (Supplementary Table 3), thus excluding a selection bias in which study completers could be a selection of the cohort with better cardiovascular adaptation to exercise.

With the aforementioned limitations, this study may contribute to cardiac rehabilitation research, in which vascular function and peripheral resistance changes could be tested as an efficacy endpoint. There may also be relevance to HFpEF, in which a component of reversible vascular dysfunction may explain the benefits observed after physical training despite unchanged cardiac function – the idea that at least some HFpEF has a significant and reversible vascular dysfunction component is not widely considered.[42,43] Additional points that need clarification are the mechanisms underlying these observations and the impact of sex on cardiovascular ageing and its interaction with physical exercise.[37,44]

In conclusion, these data show how different age groups shift on the training-induced cardiovascular remodelling spectrum, with more relevant cardiac changes observed in the youth, resembling an early athlete's heart phenotype, and more vascular changes, tending to improved efficiency through optimisation of cardiac load and corresponding to a decrease in vascular age, in the elderly.

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Author contribution

AD, ANB, ADH, GL, CHM, SS, JCM contributed to the conception or design of the work. CT, AD, JAA, ANB, KDK, AF, GB, SJ, JVZ, PS, IL contributed to the acquisition, analysis, or interpretation of data. CT drafted the manuscript. AD, ANB, GP, ADH, GL, CHM, SS, JCM critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

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Training for a First-Time Marathon Reverses Age-Related Aortic Stiffening

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ABSTRACT

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

OBJECTIVES The purpose of this study was to determine whether real-world exercise training for a first-time marathon can reverse age-related aortic stiffening.

METHODS Untrained healthy individuals underwent 6 months of training for the London Marathon. Assessment pre-training and 2 weeks post-marathon included central (aortic) blood pressure 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 [CIs]).

RESULTS A total of 138 first-time marathon completers (age 21 to 69 years, 49% male) were assessed, with an estimated training schedule of 6 to 13 miles/week. At baseline, a decade of chronological aging correlated with a decrease in Ao-A, Ao-P, and Ao-D distensibility by 2.3, 1.9, and 3.1 $\times$ 10^{-3} mm Hg^{-1}, respectively ($p < 0.05$ for all). Training decreased systolic and diastolic central (aortic) blood pressure by 4 mm Hg (95% CI: 2.8 to 5.5 mm Hg) and 3 mm Hg (95% CI: 1.6 to 3.5 mm Hg). Descending aortic distensibility increased (Ao-P: 9%; $p = 0.009$; Ao-D: 16%; $p = 0.002$), while remaining unchanged in the Ao-A. These translated to a reduction in "aortic age" by 3.9 years (95% CI: 1.1 to 7.6 years) and 4.0 years (95% CI: 1.7 to 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. (J Am Coll Cardiol 2020;75:60–71) © 2020 by the American College of Cardiology Foundation.

Aging 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

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ventricular afterload. Such changes in hemodynamics are associated with dementia and cardiovascular and kidney disease (1-3), even in the absence of atherosclerosis (4), suggesting that age-related arterial stiffening is detrimental to health. Antihypertensive 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 nonprescribed exercise, with 18 million finishers in the United States 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 (CMR), 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 aging 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.

SEE PAGE 72

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 one-half of ~50,000 receiving ballot places each year), and current participation in running for <2 h/week. In 2016, participants age 18 to 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 6 months prior to the marathon. These were repeated within 3 weeks after completion of the London Marathon, but not earlier than 1 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. A total of 237 participants were recruited; 71 did not run the marathon (52 due to injury), and 139 completers attended follow-up. One participant started antihypertensive 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/week, increasing in difficulty for a 17-week period leading into the London Marathon race (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 cardiopulmonary exercise test assessments are described in the Online Methods. After BP acquisition, CMR was performed at 1.5-T (Magnetom Aera, Siemens AG Healthcare, Erlangen, Germany). Single-shot electrocardiography-gated white blood sagittal aortic ("candy cane") views were acquired first to measure 3-dimensional 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, electrocardiography-gated, and segmented with the following parameters: acquired temporal resolution 9.2 ms (reconstructed to 100

ABBREVIATIONS AND ACRONYMS

CMR = cardiovascular magnetic resonance

DBP = diastolic blood pressure

peak VO_2 = maximal oxygen consumption

PP = pulse pressure

PWV = pulse wave velocity

SBP = systolic blood pressure

cardiac phases per RR interval); spatial resolution 1.97×1.77 mm^2; slice thickness 6 mm; through-plane velocity encoding 150 cm/s; field of view 192 × 108 mm; flip angle 20°. The contours for the ascending, proximal, and distal (diaphragmatic) descending aorta were traced semiautomatically using validated software (ArtFun, Inserm, Paris, France) on the phase-contrast modulus for area analysis and velocity images to derive velocity profiles (Online Figure 1) (18). Analysis was performed with the operator blinded to the scan timing (baseline or follow-up) and with the paired scans analyzed 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 3 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, the ß-stiffness index was also calculated. This is a pressure-independent measure of intrinsic arterial stiffness because it accounts for the nonlinear compliance to pressure relationship:

$$Distensibility = \frac{A_{max} - A_{min}}{A_{min} \times cPP \times 1000} 10^{-3} \bullet mm\,Hg^{-1}$$

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

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

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 100 mm Hg. 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, so any deviations from expected values may reflect between-subject susceptibility to accelerated aging or, conversely, vascular adaptation.

STATISTICAL ANALYSIS. Data were analyzed in R (R Foundation, Vienna, Austria) using RStudio Server version 1.0.153 (RStudio Inc., Boston, Massachusetts). All continuous variables are expressed as mean ± SD or median (interquartile range) for skewed data, and the 95% confidence interval (CI) 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 the Mann-Whitney *U* test and 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. (11). To minimize the influence of outliers, extreme data points (greater than 6 interquartile ranges below the first or above the third quartile) were removed (8 of 1,668 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 maximal oxygen consumption (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

TABLE 1 Baseline Characteristics and Follow-Up Response to Exercise, Stratified by Older (Age >37 Years) and Younger (Age ≤37 Years) Participants

	Whole Cohort			Older (>37 Years)			Younger (≤37 Years)		
	Baseline	Follow-Up	p Value	Baseline	Follow-Up	p Value	Baseline	Follow-Up	p Value
n	138			59			79		
Age, yrs	37 (21–69)			47 ± 7			30 ± 4		
Male	68 (49)			28 (47)			40 (51)		
Running time, h	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 VO_2, 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, beats/min	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, mm Hg									
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, mm Hg									
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

Values are n, median (interquartile range), mean ± SD (full age range for whole cohort), or n (%). One 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's imaging data was not saved successfully at 1 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.

DBP = diastolic blood pressure; MAP = mean arterial pressure; PP = pulse pressure; SBP = systolic blood pressure.

assumptions of constant variance and normality of residuals. All tests were 2-tailed, and a p value <0.05 was considered statistically significant. For primary endpoints, a 0.10 false discovery rate, according to the method described by Benjamini and Hochberg, was used to determine significant associations (21).

RESULTS

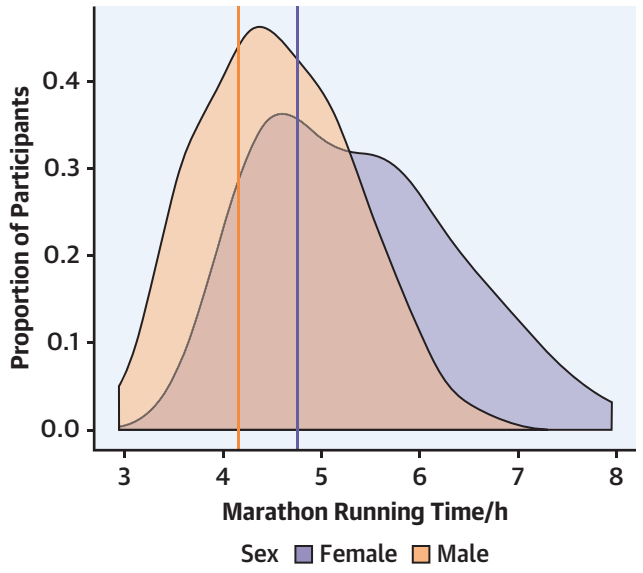
PARTICIPANTS. A total of 138 first-time marathon completers attended assessment 176 ± 11 days before and 16 ± 4 days after marathon completion. The mean age was 37 ± 10 years (range 21 to 69 years), and 49% were men. Participant characteristics at baseline and follow-up are summarized in **Table 1**. Average marathon running time was 5.4 ± 1.0 h for women and 4.5 ± 0.8 h 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/week (22).

BASELINE AGING AND AORTIC STIFFNESS. For the ascending, proximal descending, and diaphragmatic descending aorta, a decade of aging resulted in a decrease in distensibility by 2.3, 1.9, and 3.1 × 10^{-3} mm Hg^{-1} and an increase in ß-stiffness by 27%, 22%, and 16%, respectively (Online Figure 2).

EFFECT OF TRAINING ON BP AND HEART RATE. Brachial SBP and diastolic blood pressure (DBP) decreased with training by 4 mm Hg (95% CI: 2.8 to 5.5 mm Hg) and 3 mm Hg (95% CI: 1.6 to 3.5 mm Hg), respectively; p < 0.01 for both. Central SBP and DBP decreased with training by 4 mm Hg (95% CI: 2.5 to 5.3 mm Hg) and 3 mm Hg (95% CI: 1.6 to 3.5 mm Hg), respectively; p < 0.001 for both (**Figure 2**). There was no significant change in heart rate with training (−2.3 beats/min [95% CI: 0.3 to −4.3 beats/min); 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 p = 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

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.

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 years (95% CI: −0.9 to 5.4 years; $p = 0.16$), 3.9 years (95% CI: 1.1 to 7.6 years; $p = 0.009$) and 4.0 years (95% CI: 1.7 to 8.0 years; $p = 0.002$) in the ascending, proximal descending, and diaphragmatic descending aorta, respectively. When estimated from β-stiffness, biological aortic age reduced by 0 years (95% CI: −2.8 to 2.8 years; $p = 0.99$), 2.4 years (95% CI: −0.5 to 5.3 years; $p = 0.11$), and 3.2 years (95% CI: 0.1 to 6.2 years; $p = 0.04$) 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, Figure 2**). Men had a greater reduction than women 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 $p = 0.02$, 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 $p = 0.02$, 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.

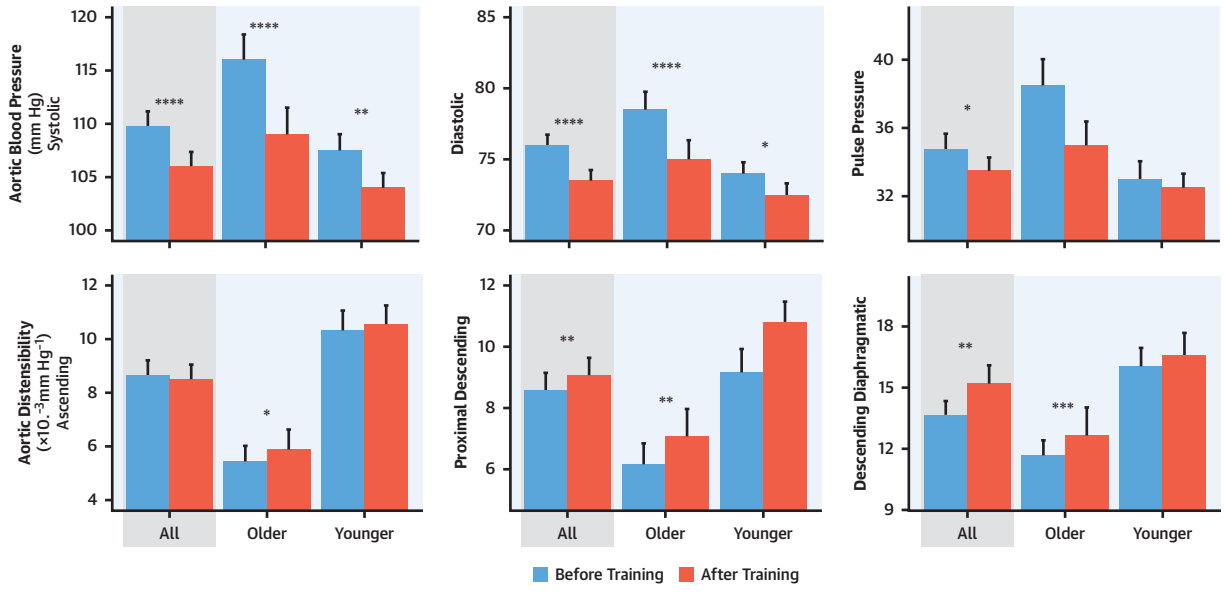
Baseline peak VO_2, heart rate, body fat, and weight or alterations in these parameters with training were not associated with the change in either measure of aortic stiffness with training.

DISCUSSION

This prospective longitudinal cohort study showed that 6 months of training and completion of a first-time marathon is sufficient to achieve reductions in blood pressure and aortic stiffness (**Central Illustration**). It was possible to reverse the consequences of aging on vessel stiffening by approximately 4 years, as measured in the aorta rather than more peripheral vessels. Both brachial and aortic SBP reduced by 4 mm Hg, a magnitude comparable to first-line antihypertensive medications (23). 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 30 min slower than the average completion time for the London Marathon. Based on completion times, participants trained for 6 to 13 miles/week, in line with the suggested 17-week training program and within the recommendations of the 2018 USA Physical Activity Guidelines (24).

In healthy individuals, chronological aging 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 (25).

FIGURE 2 **Greater Change With Exercise Training in Aortic Blood Pressure and Distensibility Is in Older Age Category Participants (Age >37 Years)**



(Top left to top right) Aortic blood pressure—systolic, diastolic, and pulse pressures. **(Bottom left to bottom right)** Aortic distensibility—ascending, proximal descending, and descending diaphragmatic. Data are medians and standard errors. *p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001.

Cross-sectional studies have shown that moderate-intensity exercise at 4 to 5 days/week preserves "youthful" compliance of the carotid artery (26). 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 programs that prescribe the type, dose, and frequency of exercise (12,27). 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 aging process, particularly as it appears "never too late" to gain the benefit as seen in older, slower runners (28).

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 that the participants in this study were normotensive and a greater improvement was observed in those with higher SBP (29). Persistent reductions in SBP of this magnitude reduce stroke mortality by over 10% and avoid large numbers of premature deaths in the general population (30). Both reductions in aortic stiffness and BP are in keeping with the magnitude of benefit from other aerobic exercise interventions (31). There was a small change in peak VO_2 that did not explain the change in stiffness, contrary to expectation, but was also observed in other studies (11,32). 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 cardiopulmonary 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 that reflection magnitude was unchanged. One study of 13 men observed similar

TABLE 2 Aortic Stiffness Before and After Exercise Training, Stratified By Older (Age >37 Years) and Younger (Age ≤37 Years) Participants

	Whole Cohort			Older (Age >37 Years)			Younger (≤37 Years)		
	Baseline	Follow-Up	p Value	Baseline	Follow-Up	p Value	Baseline	Follow-Up	p Value
n	138			59			79		
Distensibility ($\times 10^{-3}$ mm Hg^{-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	–

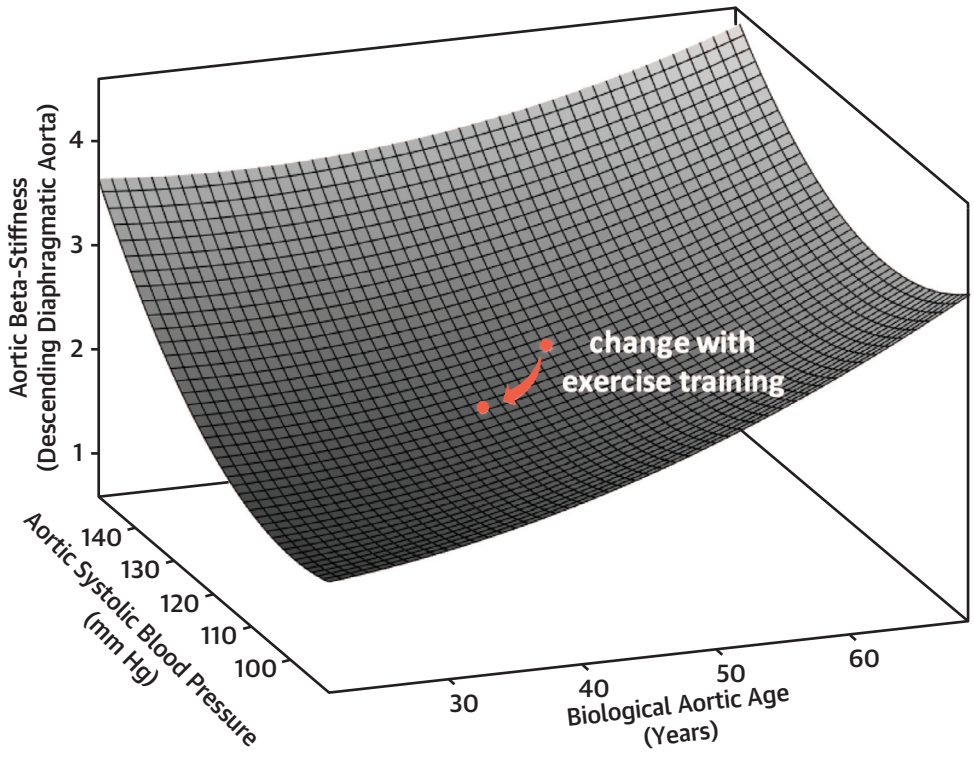
Values are n, median (interquartile range), mean ± SD. Only p values that are significant at 0.10 false discovery rate are reported.
Z_c = characteristic impedance.

benefits after just 4 weeks of training (33), but other 2- to 4-month studies observed that the reduction in stiffness was predominantly functional (34,35). Unlike previous studies, we used direct CMR assessment of the aorta 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 (32). Older, male runners had a greater reduction in aortic stiffness, attributable to greater baseline BP and aortic stiffness. Although aortic stiffening increases significantly after the age of 50 years, these data suggest that this is in part modifiable in nonhypertensive individuals (36). 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 (37). Conversely, the distal aorta media contains a higher proportion of smooth muscle that may be more readily modifiable within a 6-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 (35,38). Regional (PWV) and local (distensibility) measurement of aortic stiffness both capture this heterogeneity, but they are associated with different cardiovascular outcomes and demonstrate distinct sensitivities to downstream pathological manifestations of arterial stiffening (14,39). 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

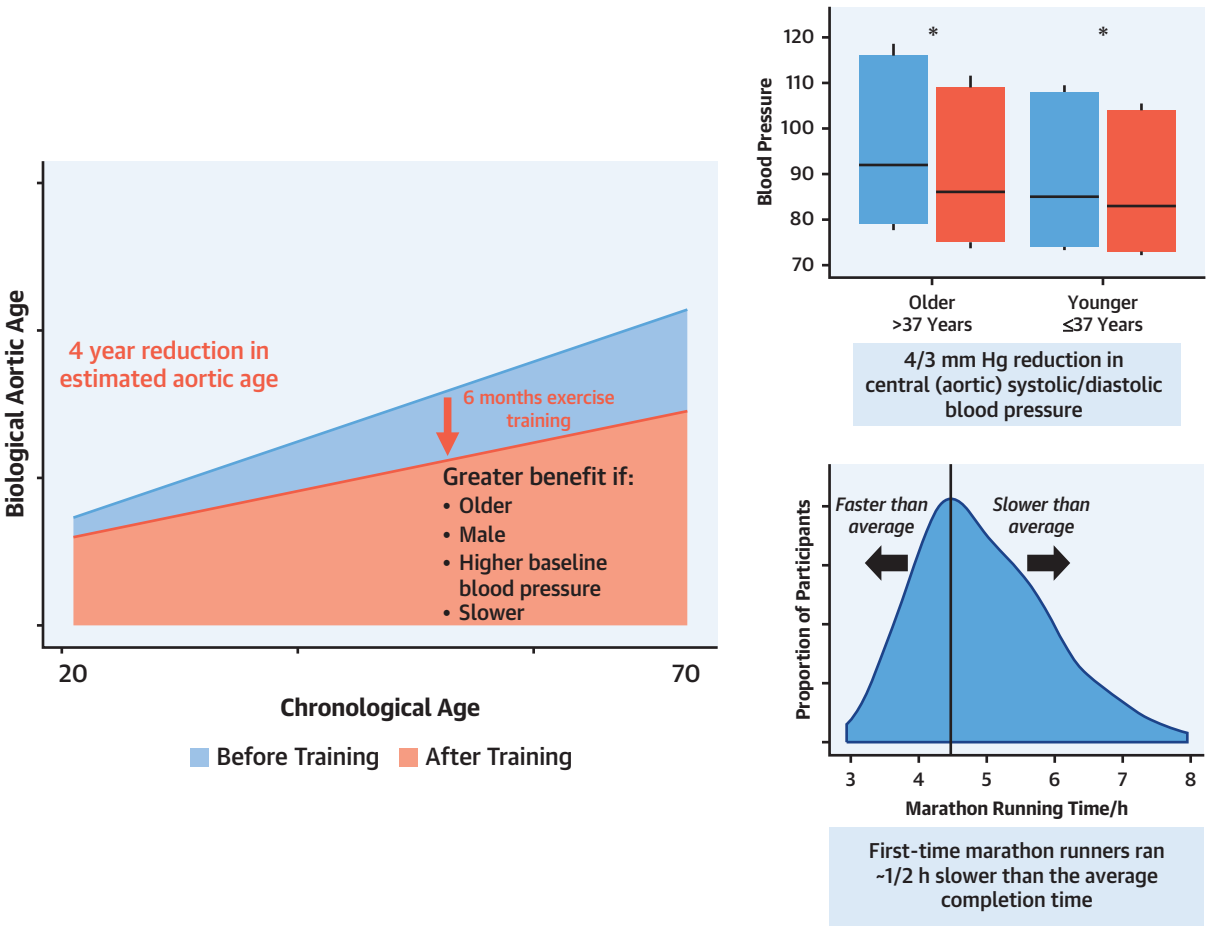
FIGURE 3 Baseline Central (Aortic) Systolic Blood Pressure, Aortic Stiffness, and Estimated Aortic Age



The **red arrow** shows the change with exercise training for the average older marathon completer.

arteries that may be less modifiable (40). 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 semisupine 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, nonfinishers 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. Although individual participants served as internal controls, there may have been run-in bias for the initial BP measurement. This appears unlikely, as BP changes would not have been age-related nor correlated with the change in separate measures (e.g., aortic stiffness) with training. Estimated aortic ages are approximations and are 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 1.5-T 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 aging (18). If error

CENTRAL ILLUSTRATION **Training and Completion of a First-Time Marathon Reverses Age-Related Aortic Stiffening and Reduces Central (Aortic) Blood Pressure**

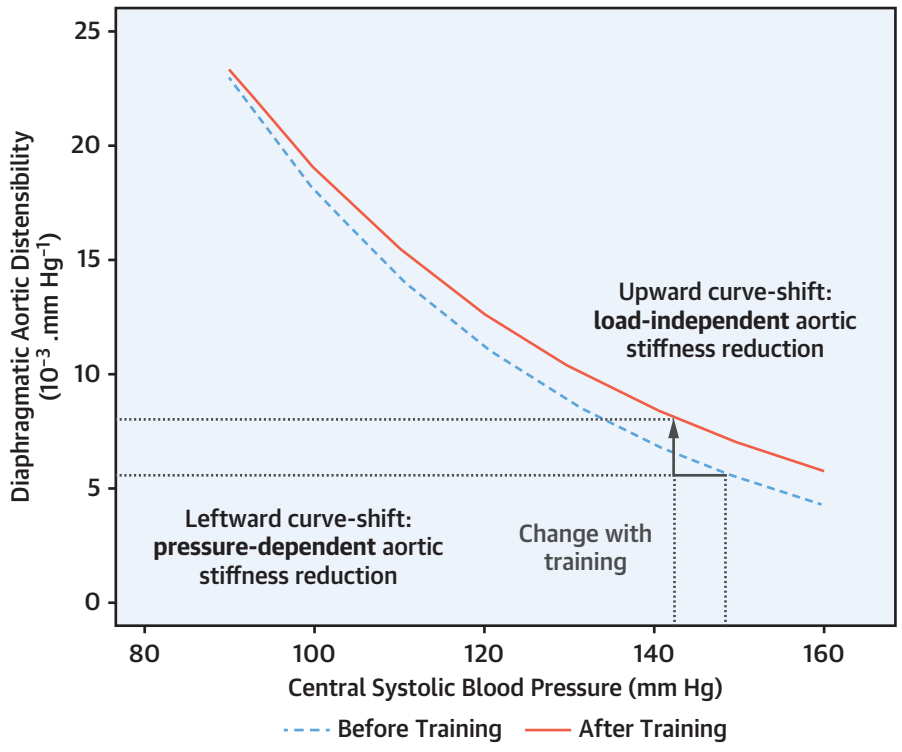


Bhuva, A.N. et al. J Am Coll Cardiol. 2020;75(1):60–71.

Biological aortic age was calculated from the baseline age-stiffness relationship at assessment 6 months before and 2 weeks after a first marathon. The reduction in aortic stiffness was equivalent to a 4-year reduction in estimated aortic age. These benefits were greater in older, male, slower runners with higher baseline systolic blood pressure, in adjusted models. Data are the linear age-stiffness relationship before and after exercise training **(left)**; systolic blood pressure, diastolic blood pressure, and mean arterial pressure **(top right)**; and marathon running times **(bottom right)**. *$p < 0.05$.

was introduced into distensibility measurements related to through-plane motion, the resultant noise would minimize 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 ~6 mm Hg higher in the descending thoracic than the ascending aorta (20). This PP amplification is not accounted for in our analysis, because it would have involved invasive measures of aortic pressure at each location. 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 published data for comparison (41). Unlike Voges et al. (41), central rather than brachial PP was used, which would explain greater distensibility, and the use of 1.5-T phase-contrast modulus may accentuate image contrast differences between 3T gradient echo sequences.

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 **(black arrows and lines).** In this schematic, data are fitted to an exponential for the cohort both before and after exercise training.

CONCLUSIONS

Training and completion of a first-time marathon result in beneficial reductions in BP and intrinsic aortic stiffening in healthy participants. These changes are equivalent to approximately a 4-year reduction in vascular age. Greater benefit was observed in older, slower, male marathon runners with higher baseline blood pressure.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Increased aortic stiffness and central aortic BP, both strong predictors of cardiovascular mortality, are lowered after 6 months of training for and completion of a first-time marathon race in healthy individuals. Older, slower men gain the greatest benefit.

TRANSLATIONAL OUTLOOK: Further studies are needed to clarify the mechanisms by which exercise influences aortic remodeling and to define training regimens that are most beneficial for vascular health.

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KEY WORDS aging, aortic stiffness, blood pressure, cardiovascular magnetic resonance, exercise training, marathon

APPENDIX For an expanded Methods section as well as supplemental figures and tables, please see the online version of this paper.

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Non-invasive assessment of ventriculo-arterial coupling using aortic wave intensity analysis combining central blood pressure and phase-contrast cardiovascular magnetic resonance

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Background Wave intensity analysis (WIA) in the aorta offers important clinical and mechanistic insight into ventriculo-arterial coupling, but is difficult to measure non-invasively. We performed WIA by combining standard cardiovascular magnetic resonance (CMR) flow-velocity and non-invasive central blood pressure (cBP) waveforms.

Methods and results Two hundred and six healthy volunteers (age range 21–73 years, 47% male) underwent sequential phase contrast CMR (Siemens Aera 1.5 T, $1.97 \times 1.77\ mm^2$, 9.2 ms temporal resolution) and supra-systolic oscillometric cBP measurement (200 Hz). Velocity (*U*) and central pressure (*P*) waveforms were aligned using the waveform foot, and local wave speed was calculated both from the PU-loop (*c*) and the sum of squares method (*c*SS). These were compared with CMR transit time derived aortic arch pulse wave velocity (PWV_{tt}). Associations were examined using multivariable regression. The peak intensity of the initial compression wave, backward compression wave, and forward decompression wave were 69.5 ± 28, -6.6 ± 4.2, and $6.2 \pm 2.5 \times 10^4\ W/m^2/cycle^2$, respectively; reflection index was 0.10 ± 0.06. PWV_{tt} correlated with *c* or *c*SS ($r = 0.60$ and 0.68, respectively, $P < 0.01$ for both). Increasing age decade and female sex were independently associated with decreased forward compression wave (-8.6 and $-20.7\ W/m^2/cycle^2$, respectively, $P < 0.01$) and greater wave reflection index (0.02 and 0.03, respectively, $P < 0.001$).

Conclusion This novel non-invasive technique permits straightforward measurement of wave intensity at scale. Local wave speed showed good agreement with PWV_{tt}, and correlation was stronger using the *c*SS than the PU-loop. Ageing and female sex were associated with poorer ventriculo-arterial coupling in healthy individuals.

Keywords wave intensity analysis • ventriculo-arterial coupling • reflection index • haemodynamics • CMR • aorta

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Introduction

An integrated assessment of the cardiovascular system is clinically and mechanistically important, yet ventricular and arterial function are often considered in isolation. Wave intensity analysis (WIA) is a technique that characterizes flow generated by the heart and the afterload imposed by the vasculature in terms of wave propagation.[1,2] It also calculates wave reflection and wave speed which predict coronary and cardiac events, independently of conventional cardiovascular risk factors.[3–8]

Waves transmit energy and arise in the circulation as a result of cardiac contraction and relaxation, or reflection. Because reflection occurs from circulatory sites of impedance mismatching, WIA describes the efficiency of energy transfer in the cardiovascular system. The magnitude of energy transferred by a wave is quantified as the product of changing pressure and flow-velocity at the same location.[9] Waves are further characterized by their direction of travel (forwards or backwards), and the pressure gradient across them (compression or decompression waves). Both these characteristics determine their impact on pressure and flow [e.g. a forward compression wave (FCW) increases pressure and accelerates flow whereas a forward decompression decreases pressure and decelerates flow]. In addition to measuring the timing and intensity of waves, WIA can quantify local wave speed, a measure of arterial stiffness.[9–12] The relationship with the reference standard of regional pulse wave velocity measured from transit time (PWV_{tt}) has not been established.

Traditionally, WIA has been derived invasively using simultaneous catheter measures of pressure and flow or velocity.[13] It has offered insights into a range of diseases but because of feasibility, understanding of healthy ageing and sex differences in the aorta has been limited.[14–17] Phase-contrast cardiovascular magnetic resonance (CMR) imaging allows non-invasive assessment of aortic flow, and CMR is the gold-standard for anatomically standardized cross-sectional measurements. CMR distensibility has successfully been used as a central pressure surrogate to perform WIA, but the method does not provide a direct measure of wave energy and can be technically challenging.[14,18] Cuff-based devices simplify the acquisition of central blood pressure (cBP) waveform data and show good agreement with invasive measures.[19]

The aims of this study were[1] to use non-invasive direct measures of the cBP and velocity waveforms to perform WIA,[2] to compare measures of local wave speed with a reference of conventionally calculated PWV_{tt}, and[3] to evaluate associations between aortic WIA and age and sex in healthy individuals.

Methods

Study population

Two hundred and thirty-seven healthy participants were recruited from the pre-training assessment of the Marathon Study. This is an observational study recruiting healthy volunteers to investigate the effects of first-time marathon training on cardiovascular function.[20] Acquisition of data for WIA did not add extra time to the standard tests performed. Inclusion criteria were age over 18 years, no past significant medical history, no previous marathon-running experience, and current participation in running for <2 h per week. 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).

A total of 211 participants underwent paired phase-contrast CMR and cBP waveform recording (Supplementary data online, *Figure S1*). Five participants were excluded due to noisy BP profiles, leaving a total 206 participants.

cBP and heart rate estimation

Supra-systolic oscillometric brachial BP was measured over 10 s with a sampling frequency of 200 Hz in duplicate after a period of rest in the semi-supine position. (Cardioscope II BP+, 6, Sydney, Australia). A single ensemble averaged central pressure estimate (*P*) was derived from the second 10 s measurement of the brachial supra-systolic arterial waveform, as previously described.[21] This has been shown to yield highly correlated central systolic BPs and pressure waveforms with invasive catheter assessment, no bias, and good intra- and re-test reliability.[21,22] Heart rate (HR) was taken as the average of the HR during the recording.

CMR acquisition and analysis

After BP acquisition, CMR was performed at 1.5 T (Magnetom Aera, Siemens AG Healthcare, Erlangen, Germany). Participants were supine for approximately half an hour of scanning before the sequence acquisitions used for this analysis. Single-shot electrocardiogram (ECG)-gated white blood sagittal aortic ('candy cane') views were acquired first, to allow 3D aortic arch length measurement and standardized cross-sectional imaging. This was used to pilot axial aortic blood flow-velocity maps at the level of the pulmonary artery bifurcation. The spoiled gradient echo phase-contrast sequence used was free-breathing, ECG-gated and segmented, with the following parameters: acquired temporal resolution 9.2 ms (reconstructed to 100 cardiac phases per RR interval); spatial resolution 1.97×1.77 mm^2; slice thickness 6 mm; through-plane velocity encoding 150 cm/s; field of view 192×108 mm; flip angle 20°.

Images were analysed using validated software to obtain velocity-time profiles for the ascending and descending aorta (ArtFun, University Pierre Marie Curie–INSERM).[23,24] The only user interaction was to select the centre and border of the lumen on the modulus imaging. A circular cross-sectional aortic lumen region of interest (ROI) was then contoured automatically and propagated to each velocity-encoded phase; automatic contours were checked and modified manually if necessary. Mean aortic velocity within each ROI was then calculated for every phase to plot a velocity-time profile. Ascending aortic velocity-time profiles (*U*) were combined with BP waveforms for WIA (*Figure 1*). *Figure 2* provides a flow chart of data acquisition and analysis.

Pulse wave velocity calculation using transit time

Aortic arch PWV was calculated from the 3D distance between the ascending and descending aortic locations of the phase-contrast imaging and the transit time between velocity profiles:

$$\text{Aortic arch } PWV_{tt} = \frac{\text{3D distance}}{\text{transit time}}.$$

Distance travelled was measured in a 3D coordinate system combining the sagittal and axial imaging using at least 14 markers placed in the centreline of the aorta. The transit time was calculated using the least squares estimate between the systolic upslopes, which has shown to be most accurate and reproducible.[25,26] Measurements were repeated by another observer in 11 cases and showed excellent intra- and inter-observer reproducibility (intraclass correlation coefficient 0.99 and 0.95, respectively).

Local wave speed estimation

The central pressure waveform (*P*) was linearly interpolated to the same sample frequency as the ascending aorta velocity data (*U*), and waveforms were aligned using the foot and early part of the systolic upstroke in

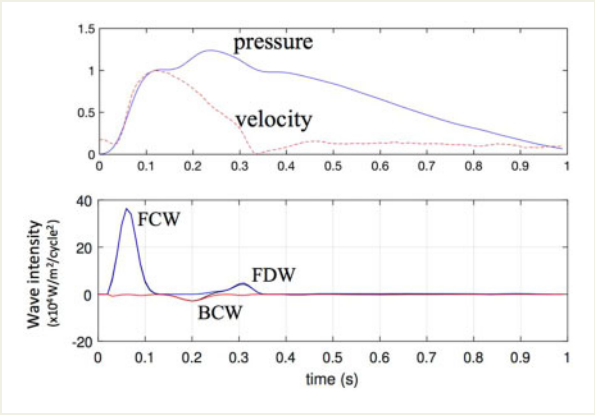

Figure 1 Aortic wave intensity analysis. Top: Foot-to-foot alignment of scaled pressure (blue) and velocity (red) waveforms. Bottom: Wave intensity analysis example showing initial compression (FCW), backward compression (BCW), and protodiastolic decompression (FDW) waves.

pressure and flow velocity (*Figure 1*). Alignment and analysis of physiological signals was performed using custom written software in Matlab R2016a (The MathWorks, Inc., Natick, MA, USA). Based on the conservation of mass and momentum, wave speed, *c*, is a function of the change in pressure and velocity described by the water-hammer equation:[10]

$$dP_{\pm} = \pm \rho c \; dU_{\pm}$$

where + refers to waves moving away from the heart, - to waves moving towards the heart, and ρ is the density of blood (1050 kg/m^3).

It is assumed that reflected waves are absent in early systole, *c* was therefore estimated as the gradient of the PU-loop at this time, *Figure 2*:

$$c = \frac{1}{\rho} \frac{dP}{dU}.$$

Wave speed can also be estimated by assuming that net wave energies are minimized over a complete cardiac cycle. This is known as the sum of squares method (*c*SS)[11] and was calculated as:

$$c\mathrm{SS} = \frac{1}{\rho} \sqrt{\frac{\sum dP^2}{\sum dU^2}}.$$

Wave intensity analysis

For WIA and *c*SS, the *P* and *U* waveforms were filtered using a standard 7 point, second order polynomial Savitzky–Golay filter to smooth data and calculate derivatives.[27] Net wave intensity was calculated as the product of the derivative of pressure (*dP*) and velocity (*dU*) over the cardiac cycle:[9]

$$dI = dP \cdot dU.$$

When wave speed is known (*c*), forward and backward wave intensity can be solved using the water-hammer equation:

$$\mathrm{WI}_{+} = \frac{1}{4\rho c}(dP + \rho c \cdot dU)^2$$

$$\mathrm{WI}_{-} = -\frac{1}{4\rho c}(dP - \rho c \cdot dU)^2$$

where WI_{+} is the forward wave intensity, WI_{-} is the backward wave intensity, and *c* is wave speed estimated using the PU-loop method.

Wave intensity was quantified using the magnitude and timing of the peak of three waves:[28] the initial FCW, backward compression wave (BCW), and forward protodiastolic decompression (expansion) (FDW) wave (*Figure 1*). To enable comparisons between subjects, the sample period was normalized by the duration of the cardiac cycle,[15] but can be converted into W/m^2/s^2 simply by multiplying by the HR per second. The reflection index was taken as the ratio of BCW/FCW.[17] Wave energy was calculated as the area under each wave. For comparison, wave separation analysis was performed to calculate the reflection magnitude, taken as the ratio of the peak backward to the peak forward pressure amplitudes.[2]

Anthropomorphic and other assessments

Height was recorded using a standard stadiometer. Weight and body fat percentage were measured using digital bioimpedance scales (BC-418, Tanita, USA). Body surface area was calculated using the Mosteller formula. Maximal oxygen consumption (peak VO_2) was estimated by a cardio-pulmonary exercise test on a semi-supine ergometer (Ergoselect1200, Ergoline, Germany) using an incremental protocol standardized by bodyweight and gender, as previously described.[20]

Statistics

Data were analysed in R (R foundation, Vienna, Austria) using RStudio Server version 0.98 (Boston, MA, USA). All continuous variables are expressed as mean ± SD or median (interquartile range) for skewed data. Normality was checked using the Shapiro–Wilk test. Categorical variables are expressed as percentages. Characteristics are stratified by age decile and gender. Groups were compared using independent-samples Student's *t*-tests for normally distributed continuous variables or Mann–Whitney *U* tests and χ^2 tests for non-normally distributed and categorical variables, respectively. For trends over age deciles, the non-parametric Mann–Kendall monotonic trend test was used. Pearson's correlation coefficient (*r*) and Bland–Altman limits of agreement (LoA) were used to assess correlation and agreement, respectively. Multivariable linear regression models for the association between age and WIA parameters were adjusted for covariates that a priori could confound the relationship; these were sex, HR, and height; similarly, sex was adjusted for age, HR, and height. Mean arterial pressure was not included as it may be dependent on wave generation rather than the converse.[29] Regression diagnostics were performed and data were log-transformed if appropriate. All tests were two tailed, and $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

In 206 healthy volunteers, the median age was 37 years (range 21–73 years), 189 (92%) were normotensive (<140/90 mmHg) on assessment; and mean aortic arch $\mathrm{PWV_{tt}}$ was 4.7 ± 1.5 m/s, *Table 1*. The peak intensity of the initial compression wave, BCW, and FDW were 69.5 ± 28, -6.6 ± 4.2, and 6.2 ± 2.5 × 10^4 W/m^2/cycle^2, respectively; reflection index was 0.10 ± 0.06.

Local wave speed compared to $\mathrm{PWV_{tt}}$

There was a moderate correlation between $\mathrm{PWV_{tt}}$ and *c*, and this was stronger with *c*SS ($r = 0.60$ and 0.68, respectively, $P < 0.01$ for both). $\mathrm{PWV_{tt}}$ was greater than *c*, and this difference was reduced for *c*SS [difference: -1.3 (LoA: -3.8 to 1.2) vs. -0.64 (LoA: -3.0 to 1.7) m/s, respectively; *Figure 3*].

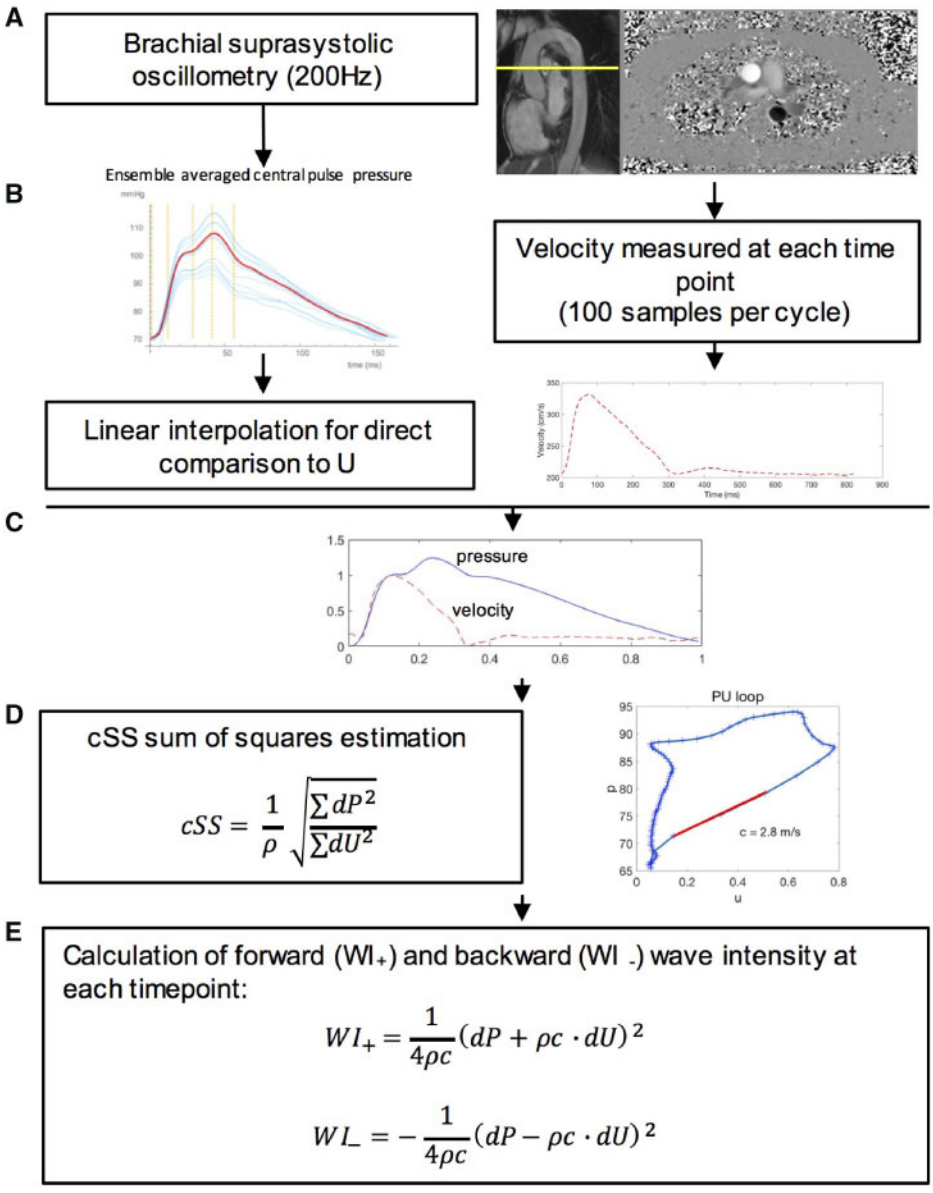

Figure 2 Analysis of blood pressure and CMR-derived velocity data. (*A*) After a period of rest the patient underwent oscillometric brachial blood pressure on two occasions immediately prior to MRI. A Pulsecor BP+ device acquired 10 s of brachial waveforms at 200 Hz. After, phase-contrast MRI was acquired at the level of the pulmonary artery using a free-breathing ECG-gated sequence, acquired at c.100 Hz at 60 bpm. (*B*) A single ensemble averaged central pressure (*P*) was estimated and velocity (*U*) measured at each time point. (*C*) Data were aligned by waveform foot to foot. (*D*) Wave speed measured in early systole using the pressure-velocity loop and sum of squares method after the application of a Savitzky–Golay filter. (*E*) Wave intensity calculated using the derivatives of pressure and velocity. ρ, density of blood (1050 kg/m^3); *c*, *P-U* derived wave speed; *c*SS, sum of squares estimated *c*.

Wave speed and wave intensity by age decade

Both *c* and *c*SS increased from youngest (20–30 year old) to oldest (≥60 year old) age decade (*Figure 4*), although *c*SS tended to be higher than *c*. *Table 2* displays all WIA measures stratified by age decade and sex.

FCW decreased progressively with age up to 50–60 year old, but rose in ≥60 year old. The BCW increased steadily from youngest to oldest age decade. This resulted in a steady increase in reflection index with age decade. There was no convincing trend in FDW with age. Age-related trends were not modified by sex, so data for both sexes are pooled in *Figure 4*.

Associations of wave intensity after adjustment for potential confounders

In multivariable analysis including age, sex, HR, and height as covariates, older age was associated with a smaller FCW, a larger BCW, and a larger reflection index. Male sex was associated with a higher

Table 1 Study participant characteristics stratified by sex and age decile

Participant characteristics	Males					Females				
	20–30	30–40	40–50	50–60	60+	20–30	30–40	40–50	50–60	60+
n	31	31	22	9	3	33	35	30	9	3
Age (years)	26 ± 2	32 ± 2	44 ± 3	54 ± 2	66 ± 4	26 ± 2	33 ± 3	45 ± 3	54 ± 2	67 ± 6
Height (cm)	181 ± 7	181 ± 7	180 ± 6	177 ± 9	172 ± 4	167 ± 5	167 ± 5	167 ± 6	169 ± 5	160 ± 5
Weight (kg)	78 ± 8	82 ± 15	85 ± 9	81 ± 15	76 ± 7	63 ± 9	69 ± 11	69 ± 15	71 ± 13	70 ± 16
BMI (kg/m^2)	24 ± 3	25 ± 4	26 ± 3	26 ± 4	26 ± 2	22 ± 3	25 ± 4	25 ± 5	25 ± 5	27 ± 5
BSA (m^2)	2.0 ± 0.1	2.0 ± 0.2	2.0 ± 0.1	2.0 ± 0.2	1.9 ± 0.1	1.7 ± 0.1	1.8 ± 0.1	1.8 ± 0.2	1.8 ± 0.1	1.7 ± 0.2
Body fat (%)	15 ± 5	20 ± 6	23 ± 5	22 ± 6	23 ± 2	28 ± 6	32 ± 7	32 ± 8	33 ± 8	35 ± 7
Peak VO_2 (mL/kg/min)	43 ± 6	38 ± 6	33 ± 6	34 ± 7	25 ± 3	35 ± 4	32 ± 6	29 ± 7	24 ± 4	24 ± 3
Resting heart rate (bpm)	70 ± 15	70 ± 15	72 ± 14	67 ± 14	64 ± 4	74 ± 15	71 ± 10	69 ± 12	67 ± 12	67 ± 11
Brachial SBP (mmHg)	124 ± 11	124 ± 12	128 ± 10	133 ± 18	146 ± 19	113 ± 8	113 ± 10	117 ± 13	127 ± 20	136 ± 33
Brachial DBP (mmHg)	75 ± 4	75 ± 6	79 ± 5	79 ± 7	79 ± 10	72 ± 5	73 ± 6	74 ± 7	80 ± 10	76 ± 18
Aortic SBP (mmHg)	113 ± 10	113 ± 10	117 ± 9	124 ± 19	136 ± 23	104 ± 8	106 ± 10	109 ± 11	122 ± 19	129 ± 31

BMI, body mass index; BSA, body surface area; DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure; Peak VO_2, maximal oxygen consumption.

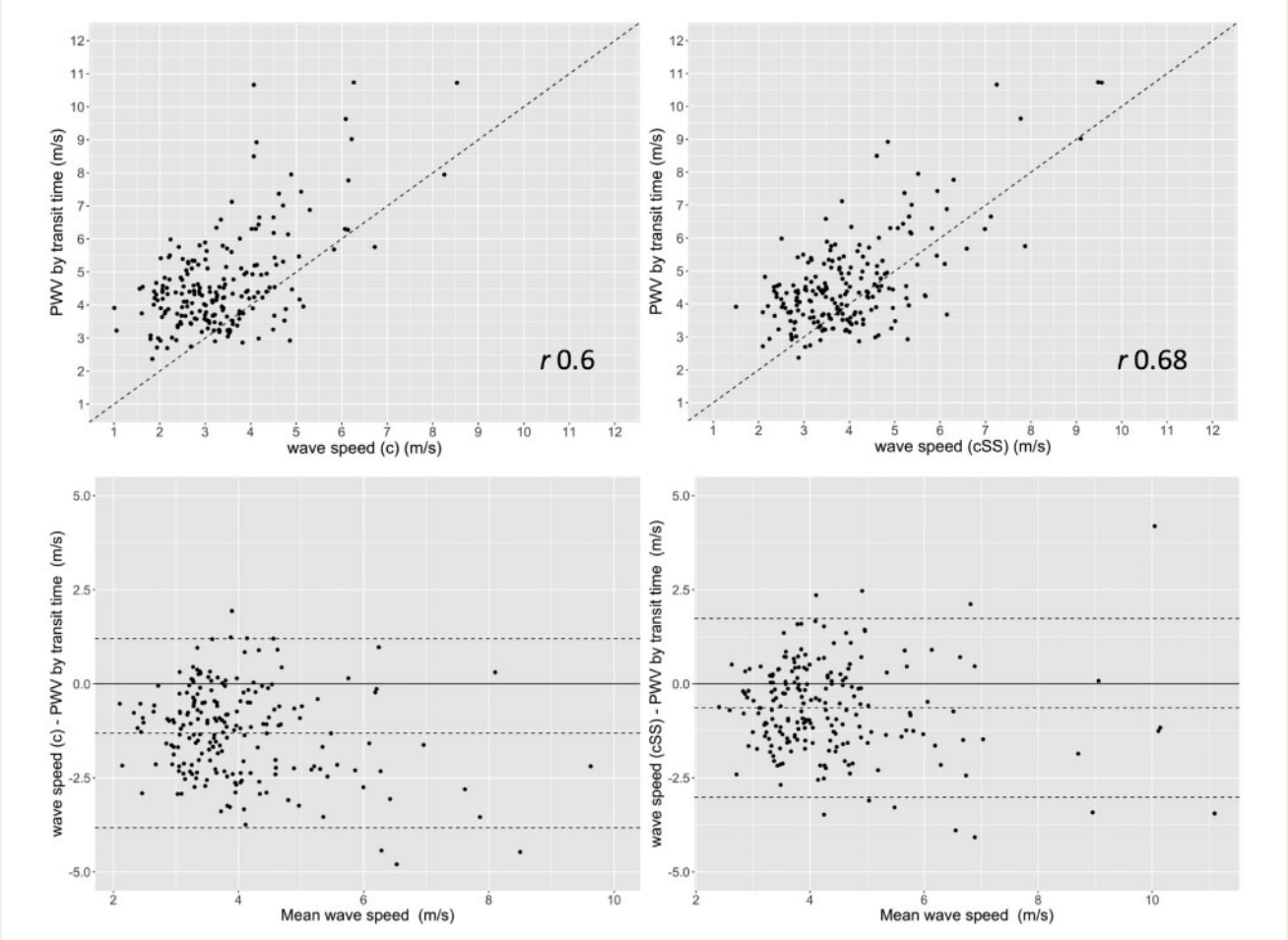

Figure 3 Correlation (top row) and Bland–Altman analysis (bottom row) of wave speed and pulse wave velocity (PWV) measured by transit time. Left: wave speed calculated from the pressure-velocity slope during early systole (*c*). Right: wave speed calculated from the sum of squares method (*cSS*). The dotted line in the upper two panels indicates the line of unity. In the lower two panels the dotted lines indicate the mean difference and the limits of agreement.

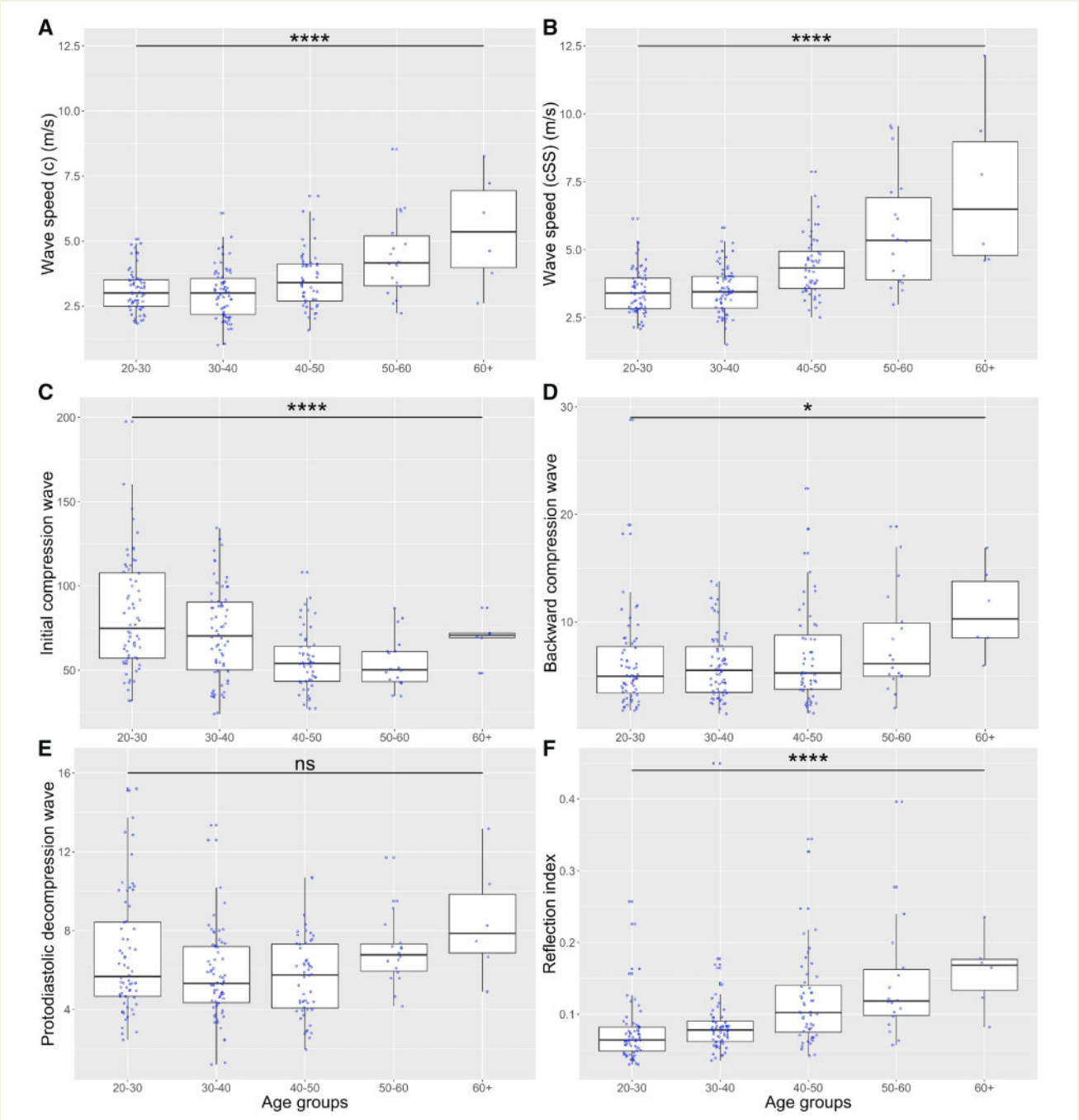

Figure 4 Influence of age on wave speed and wave intensity indices. (*A*) Wave speed (*c*) measured by PU-loop. (*B*) Wave speed measured by sum of squares method (*c*SS). (*C*) Forward compression wave. (*D*) Backward compression wave. (*E*) Forward decompression wave. (*F*) Reflection index. ns: $P > 0.05$, *$P < 0.05$, ****$P < 0.0001$.

FCW, no difference in BCW and consequently a lower reflection index, and a higher FDW compared with females. Higher HR was associated with a lower FCW, a lower BCW, a lower reflection index, and a lower FDW. Height was not associated with any WIA parameter in adjusted models. Associations between WIA and peak VO_2, and body fat are detailed in Supplementary data online, *Tables S1 and S2*.

Discussion

This is the first study to determine wave intensity and local wave speed by combining direct non-invasive measures of cBP and velocity data from phase contrast CMR. This straightforward method allows aortic WIA to be performed at scale, here in the largest cohort reported to date. This technique was validated by showing good

Table 2 Wave intensity analysis stratified by sex and age decile

Wave intensity measures	Males					Females				
	20–30	30–40	40–50	50–60	60+	20–30	30–40	40–50	50–60	60+
Wave speed (ms^{-1})										
c	3.4 ± 0.9	3.3 ± 1.1	3.9 ± 1.2	4.9 ± 2.0	5.7 ± 1.8	2.7 ± 0.6	2.7 ± 0.8	3.3 ± 1.0	4.0 ± 1.0	5.2 ± 2.9
cSS	3.4 ± 0.9	3.6 ± 0.9	4.6 ± 1.2	5.8 ± 2.3	7.3 ± 2.4	3.0 ± 0.7	3.5 ± 0.8	4.3 ± 1.1	5.5 ± 2.0	7.3 ± 4.2
Pulse wave velocity (m/s)	4 ± 0.7	4 ± 0.7	5 ± 1.1	7 ± 1.8	9 ± 3.4	4 ± 0.6	4 ± 0.6	5 ± 0.9	8 ± 2.1	7 ± 1.6
Wave peak (10^4 $W/m^2/cycle^2$)										
FCW	99 ± 35	84 ± 27	61 ± 23	62 ± 17	71 ± 1	67 ± 22	61 ± 24	52 ± 14	47 ± 9	68 ± 19
BCW	7.0 ± 4	5.9 ± 3	6.1 ± 4	8 ± 5	11.6 ± 6	5.3 ± 5	6.0 ± 4	7.4 ± 5	7.7 ± 5	10.5 ± 3
FDW	8.4 ± 3	6.7 ± 2	6.2 ± 2	7.5 ± 3	10.3 ± 3	5.2 ± 2	4.8 ± 2	5.2 ± 2	6.5 ± 1	6.6 ± 2
Wave timing (ms)										
FCW	50 ± 5	50 ± 7	52 ± 4	53 ± 3	56 ± 3	49 ± 5	48 ± 4	51 ± 5	53 ± 2	53 ± 2
BCW	152 ± 32	163 ± 24	169 ± 14	164 ± 11	162 ± 8	158 ± 19	154 ± 28	157 ± 32	167 ± 8	164 ± 6
FDW	258 ± 38	268 ± 40	275 ± 26	303 ± 48	303 ± 19	272 ± 40	272 ± 45	296 ± 27	311 ± 25	306 ± 33
Reflection index	0.06 ± 0.03	0.07 ± 0.02	0.10 ± 0.04	0.12 ± 0.05	0.16 ± 0.08	0.07 ± 0.05	0.10 ± 0.07	0.14 ± 0.07	0.17 ± 0.11	0.16 ± 0.03
Reflection magnitude	0.54 ± 0.1	0.55 ± 0.1	0.58 ± 0.1	0.56 ± 0.1	0.59 ± 0.1	0.55 ± 0.1	0.57 ± 0.1	0.61 ± 0.1	0.59 ± 0.1	0.61 ± 0.1
Wave energy (*J*)										
Forward wave	5.6 ± 1.6	4.6 ± 1.4	3.6 ± 1.0	3.5 ± 0.7	4.6 ± 0.5	3.5 ± 1.1	3.5 ± 1.2	3.0 ± 0.6	2.9 ± 0.4	4.3 ± 1.0
Backward wave	0.74 ± 0.4	0.67 ± 0.2	0.65 ± 0.3	0.70 ± 0.4	1.05 ± 0.4	0.58 ± 0.4	0.67 ± 0.3	0.71 ± 0.4	0.73 ± 0.3	1.13 ± 0.4

Pulse wave velocity was measured conventionally in the aortic arch from transit time.
c, wave speed measured by the pressure-velocity loop; *cSS*, wave speed measured by the sum of squares method; BCW, backward compression wave; FCW, forward compression wave; FDW, forward decompression wave; J, joules.

agreement between local wave speed (calculated from combined non-invasive pressure and phase contrast CMR-derived flow data) and conventionally measured pulse wave velocity using transit time. WIA patterns and magnitude appeared similar to invasive data,[13,30,31] but here the non-invasive nature of testing permitted exploration of healthy ventriculo-arterial coupling. The resolution was sufficient to detect that ageing and female sex were independently associated with decreased FCW energy and an increased proportion of wave reflection, suggesting a less energy efficient cardiovascular system.

How can non-invasive aortic WIA be used?

A similar pattern of wave intensity was found in all individuals, which can help to improve our understanding of pulsatile haemodynamics. We observed a dominant FCW in the early phase of LV ejection, which has been associated with myocardial contractility, and a smaller FDW, associated with the time constant of LV relaxation.[32] A BCW was also observed which is thought to relate to reflected waves originating from distal sites of impedance mismatch.[31] These patterns and wave timings are similar to invasive studies, but an earlier BCW compared to other non-invasive data may reflect population characteristics or quantification differences (wave foot vs. peak).[14,30,33]

Describing pressure and flow changes together, WIA has advanced the way we understand ventricular function and arterial coupling in different pathologies. Patients with chronic heart failure have an impaired ability to generate a systolic FCW, but the FCW undergoes more reflection, increasing afterload.[34] Wave intensity can predict left ventricular ejection fraction recovery or quality of life improvement in patients undergoing valvular surgery, and help to identify sub-clinical systolic and diastolic dysfunction in children with heart failure and preserved ejection fraction.[35–37] Increased wave reflection is associated with outcomes in systemic hypertension,[4] and in the pulmonary circulation is an early and specific marker in the development of pulmonary hypertension.[15,38,39] Due to reliance on invasive measures, most of these previous insights have been derived from studies of small patient cohorts. Non-invasive approaches have the potential to improve our understanding of cardiovascular haemodynamics in health and disease, and can be applied to longitudinal studies.

WIA at scale using central measures

Whilst central haemodynamics have most impact on the ventricle, previous non-invasive studies of WIA have typically been in peripheral arteries because they are easier to interrogate using Doppler ultrasound and arterial tonometry.[4,32] The approach developed in this study uses measures of central pressure and velocity rather than surrogates such as distensibility, which are dependent on aortic stiffness. Like other methods,[16] these data were acquired sequentially, but simultaneous acquisition is feasible in future studies using longer tubing for the cBP cuff measurement. This would enable the oscillometric device to be situated in the MRI control room for pressure measurement, whilst the patient has flow measured in the MRI scanner.

Local wave speed estimation

The validity of two single-point methods of wave speed were tested by comparing with a conventional regional estimate extending across the aortic arch (PWV_{tt}).[14] We used two previously described single-point methods, one based on the pressure-velocity loop[10] and

the other using the sum-of-squares method.[11] Both showed acceptable agreement with the transit time-based method which was assumed to be the reference, although agreement was slightly better for *c*SS which is consistent with the findings of a previous *in vitro* study.[40] Because wave speed increases distally, both measures of ascending aortic local wave speed were expectedly lower than regional PWV_{tt} which extends to the aortic arch.

Associations between sex or age and aortic WIA

These data show that females have a greater wave reflection index in the aorta and lower FDW magnitude, which has not been reported previously, to our knowledge. Consistent with Li *et al.*[14], females also demonstrated a smaller FCW. Borlotti *et al.*[17] found a sex difference in the reflection index in carotid but not femoral arteries, however, wave reflection in the aorta is different to that seen in the carotid. Differences in wave reflection may provide a substrate for the development of heart failure.[41]

The increase in wave speed and arterial stiffness with age are well recognized, however, age-related changes in aortic WIA measures have only previously been described in one study, which used diameter rather than pressure measurements to derive an alternative index of wave intensity.[14] The study also reported a decrease in FCW, BCW and an increase in reflection index but reported a decrease in FDW rather than the lack of change seen in this cohort. Differences with these data may be due to different study populations, or the use of diameter as a surrogate measure of pressure in the previous study, which itself is inversely related to wave speed. The proportion of reflection increased with age whether measured by wave separation or WIA. The contribution of higher intensity waves appears more pronounced at older ages and higher degrees of overall reflection. This suggests that the greater reflection that occurs with healthy ageing presents a more adverse load on the heart.[42]

Study limitations

Because data were acquired over several cardiac cycles and ensemble averaged, the average cycle is truncated leading to a slight shortening of the duration of diastole; however, since wave intensity in end-diastole is negligibly small this is unlikely to affect our findings. Participants were recruited based on their intention to participate in a first marathon, and while they were not engaged in training at the time of study it is unlikely that they are representative of the general population. Older participants were relatively under represented and are probably biased through selective recruitment of more healthy individuals. Similarly, patients were excluded with any known significant medical problems including hypertension or diabetes mellitus. We used a free-breathing phase-contrast CMR sequence which provides sufficient spatio-temporal resolution for the velocity profile. A similar sequence has also been used to measure CMR distensibility as a surrogate for central pressure, but because it is free-breathing this may compromise accuracy for measures of compliance due to through-plane motion.[33] Breath-held sequences are possible using an accelerated spiral sequence but can be difficult to analyse due to respiratory artifact or lower signal to noise.[43] Haematocrit differences between sexes were not accounted for, although this is unlikely to affect blood density significantly.

Conclusion

This article describes a novel non-invasive method for WIA, using cBP and CMR velocity data. Local wave speed measured by this technique showed good agreement with regional PWV and the method has straightforward application for large sample sizes. In healthy individuals, women had a smaller FCW and poorer overall ventriculo-arterial coupling than men. In both sexes, older age was associated with higher wave speed and poorer ventriculo-arterial coupling as assessed by WIA.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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ORIGINAL RESEARCH
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Cardiovascular Remodeling Experienced by Real-World, Unsupervised, Young Novice Marathon Runners

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Aims: Marathon running is a popular ambition in modern societies inclusive of non-athletes. Previous studies have highlighted concerning transient myocardial dysfunction and biomarker release immediately after the race. Whether this method of increasing physical activity is beneficial or harmful remains a matter of debate. We examine in detail the real-world cardiovascular remodeling response following competition in a first marathon.

Methods: Sixty-eight novice marathon runners (36 men and 32 women) aged 30 ± 3 years were investigated 6 months before and 2 weeks after the 2016 London Marathon race in a prospective observational study. Evaluation included electrocardiography, cardiopulmonary exercise testing, echocardiography, and cardiovascular magnetic resonance imaging.

Results: After 17 weeks unsupervised marathon training, runners revealed a symmetrical, eccentric remodeling response with 3–5% increases in left and right ventricular cavity sizes, respectively. Blood pressure (BP) fell by 4/2 mmHg ($P < 0.01$) with reduction in arterial stiffness, despite only 11% demonstrating a clinically meaningful improvement in peak oxygen consumption with an overall non-significant 0.4 ml/min/kg increase in peak oxygen consumption ($P = 0.14$).

Conclusion: In the absence of supervised training, exercise-induced cardiovascular remodeling in real-world novice marathon runners is more modest than previously

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described and occurs even without improvement in cardiorespiratory fitness. The responses are similar in men and women, who experience a beneficial BP reduction and no evidence of myocardial fibrosis or persistent edema, when achieving average finishing times.

Keywords: cardiovascular remodeling, athlete's heart, sports cardiology, endurance exercise, cardiorespiratory fitness, marathon

INTRODUCTION

"If you want to run, run a mile. If you want to experience a different life, run a marathon" Emil Zátopek, Olympic long-distance runner.

Running a marathon is an increasingly popular personal challenge for many non-athletes, often with the intention of fundraising for good causes. Approximately 349,000 people across Europe and 414,000 people across North America take part in marathon races every year (Andersen, (2014–2017)). The London Marathon is the third largest in the world (Andersen, (2014–2017)) and currently generates over £60 million/year in charity donations (London Marathon sets another record, 2017). London Marathon runners require no prior experience and there is no qualifying time as a barrier to race entry, with the majority taking part as first time marathon runners (Cave and Miller, 2016).

In the 1970s, it was proposed that the type of person capable of completing a marathon might acquire immunity to atherosclerosis (Bassler, 1977, 1978). It has since been made clear that this is not the case and in fact undertaking vigorous physical activity is associated with a transient 5.9 relative risk of myocardial infarction (Mittleman et al., 1993) and 16.9 relative risk of sudden cardiac death (Albert et al., 2000). The absolute risk of sudden cardiac arrest during a marathon is low at 1.01 per 100,000 participants (Kim et al., 2012) and can paradoxically be reduced by greater habitual vigorous exercise (Siscovick et al., 1984; Mittleman et al., 1993; Albert et al., 2000; Chugh and Weiss, 2015). Over the last two decades, multiple studies have highlighted potential cardiovascular dangers of marathon running including transient left and right ventricular dysfunction (Neilan et al., 2006a; La Gerche et al., 2012; Gaudreault et al., 2013), myocardial injury with release of cardiac troponin (Neilan et al., 2006a; Shave et al., 2010; Lara et al., 2019) and for those engaging repeatedly, myocardial fibrosis (Möhlenkamp et al., 2008; Breuckmann et al., 2009; Wilson et al., 2011; Tahir et al., 2018), coronary calcification (Aengevaeren et al., 2017; Merghani et al., 2017), and arrhythmias (Heidbuchel et al., 2003; Mont et al., 2009).

Despite these reported dangers, each year over 400,000 people apply to the ballot hoping to secure a London Marathon place (McGuire, 2018). Large observational data would suggest that for every hour invested in running, there is a return of 7 h longevity (Lee et al., 2017). Some studies show no ceiling of benefit but progressively diminishing returns with increasing volumes of physical activity (Wen et al., 2011; Kyu et al., 2016; Lear et al., 2017), while others describe a reverse J-shaped curve where potential harm emerges at greater than 10-fold the recommended minimum physical activity levels (Lee et al., 2014; Arem et al., 2015; Armstrong et al., 2015; Schnohr et al., 2015).

It remains debatable whether preparation for and participation in a 42-km (26-mile) footrace constitutes a healthy promotion of increased regular physical activity or a potentially cardiotoxic dose of strenuous exercise (Predel, 2014). Previous studies characterizing the remodeling changes associated with a marathon run have been limited by small sample size (Mousavi et al., 2009; Gaudreault et al., 2013; Arbab-Zadeh et al., 2014), exclusion of participants who did not adhere to structured training plans (Zilinski et al., 2015) or included supervised preparatory training for a much longer period than most typical runners would undertake (Arbab-Zadeh et al., 2014). For these reasons, our current knowledge of exercise-induced cardiovascular remodeling resulting from marathon training is somewhat skewed. Given the popularity of marathon running in modern societies, it is valuable for clinicians, runners, and prospective marathon runners to gain greater understanding of the cardiovascular changes resulting from a single marathon in real-world novice runners, for whom this may represent the greatest athletic feat of their lives. Increasing the generalizability of our findings to real-world novice marathon runners, participants were not excluded for not returning training logs or for failing to follow training plans.

The aim of this study was to assess cardiovascular remodeling in detail occurring in real-world, typical novice marathon runners, inclusive of all those finishing the race, without exclusion of those non-adherent to training programs. We sought to recruit a sufficient proportion of men and women to explore gender differences. In recognition that occult atherosclerotic coronary artery disease is an important confounding factor to outcomes of interest, we restricted our study to subjects aged 18–35 years. This group harbors a low prevalence of atherosclerotic disease and greater cardiorespiratory trainability (Ogawa et al., 1992; Green and Crouse, 1993). We hypothesized that real-world cardiovascular remodeling in unsupervised, novice marathon runners would be more modest than previously described work involving supervised marathon training and that similar responses would be seen in men and women.

MATERIALS AND METHODS

Study Design and Study Population

The study was a prospective observational study. Subjects were considered for inclusion if they were aged 18–35 years

old and had never run a marathon distance previously. Individuals were excluded if they had pre-existing cardiovascular disease during preliminary investigations or contraindication to cardiac magnetic resonance (CMR). Novice marathon runners within the specified age range, totaling 4,170, were identified through the database records of the organizers (Virgin Money London Marathon) and received notification of the study through a targeted e-mail advertisement 2 weeks after notification of their place in the 2016 London Marathon. The London Marathon is run over a predominantly flat course, through the capital city center around the river Thames, covering 42.2 km (26 miles and 385 yards). The race organizers received 247,069 applicants for ballot places in 2015 with 51,000 places given, culminating in 39,140 marathon finishers in 2016. Interested runners made contact through a call center and those fulfilling inclusion the criteria were subsequently contacted by telephone and appointed to a study day for recruitment. Written consent was obtained from all participants and the National Research Ethics Service; Queen Square, London committee granted ethical approval (15/LO/086). The trial is registered on ClinicalTrials.gov, number NCT02568072.

Testing took place in two parallel identical circuits where subjects were changed into gowns (to ensure that no ferromagnetic materials were taken into the CMR environment), height and weight were recorded, followed by cannulation and venipuncture prior to CMR. Subjects then underwent a resting echocardiogram, followed by electrocardiography and blood pressure (BP) measurement. Finally, subjects underwent cardiopulmonary exercise testing using a semi-recumbent tilting cycle ergometer combined with echocardiography in their exercise clothes (**Figure 1**). Testing was consistent between subjects and between visits.

Running Training

Subjects were encouraged to follow a beginner's training plan, consisting of approximately three runs per week, increasing in difficulty over a 17-week period leading up to the London Marathon race, which is the recommendation of the race organizers (London Marathon, 2018) (Beginner 17 Week Training Plan in **Supplementary Data Sheet S1**). Subjects wishing to follow alternative, higher intensity training plans were not discouraged from doing so.

Allometry, Bioimpedance, and Blood Pressure

Height was recorded using a standard stadiometer. Weight and body fat percentage were measured using digital bioimpedance scales (BC-418, Tanita, United States). Peripheral and central BPs were measured after 5 min of rest in accordance with international standards (Williams et al., 2004), supra-systolic oscillometric BP was measured in both arms over 10 s at 200 Hz in a semi-supine position using a Cardioscope II BP + device (USCOM, Sydney, NSW, Australia), which employs an upper arm cuff, as previously described (Costello et al., 2015). An ensemble averaged central pressure estimate was derived from the brachial BP and supra-systolic arterial waveforms to estimate central systolic and diastolic BP. At baseline, if the right arm BP was > 10 mmHg greater than the left arm this was used, otherwise the left arm BP was used and repeated measurements of BP used the same arm as the baseline measurement. All BP measurements were recorded by the same investigator (RB) supported by one of five cardiac research nurses working a rotational day schedule, all receiving the same training on recording BP using the Cardioscope II BP + device.

Electrocardiography

Two-minute ECG recordings were acquired digitally (CardioSoft, GE Healthcare, Milwaukee, WI, United States) according to internationally accepted practices (Eldridge et al., 2014).

Echocardiography

Resting and exercise two-dimensional echocardiography was performed (Vivid E9, GE Vingmed Ultrasound, Horten, Norway) with standard cardiac views obtained and analyzed according to contemporary European Association of Cardiovascular Imaging guidelines (Lang et al., 2015). Mean frame rates ranged from 72 ± 11 to 78 ± 11 frames/s for long- and short-axis views, respectively. Five cardiac cycles were stored in a cineloop format, optimized for offline 2D speckle-tracking echocardiographic analysis. All automatic image enhancement and harmonics were enabled. Images were saved digitally for subsequent offline analysis by speckle tracking analysis with dedicated software using automated function imaging (EchoPAC Version 113, GE Vingmed Ultrasound AS, Horten, Norway). Twist and torsion were calculated as previously described (Kinova et al., 2018). Studies were performed by nine accredited and experienced cardiac physiologists working a rotational day schedule. Measurements were made by a single investigator (AD) utilizing edge detection software (Auto-EF) for calculation of ventricular volumes and visual confirmation with correction where endocardial border definition was sub-optimal.

Cardiovascular Magnetic Resonance (CMR)

Cardiac magnetic resonance scans were performed using a 1.5 T magnet (Aera, Siemens Medical Solutions). LV and RV function, volumes, and myocardial mass (excluding papillary muscles) were assessed by cine steady-state free precession sequences and analyzed by a single investigator (AD) using Circle CVI42 (Circle Cardiovascular Imaging Inc., Calgary, Canada) semi-automated software including tissue tracking for strain analysis. Left and right atrial EDV and ESV were derived by manually tracing endocardial atrial contours, as previously described (Petersen et al., 2017). Studies were performed by five experienced radiographers and five experienced clinical research fellows working a rotational day schedule.

Late gadolinium enhancement (LGE) images were obtained 10 min after the intravenous bolus injection of 0.1 mmol/kg gadolinium-based contrast (gadoterate meglumine, Dotarem, Guerbet, LLC).

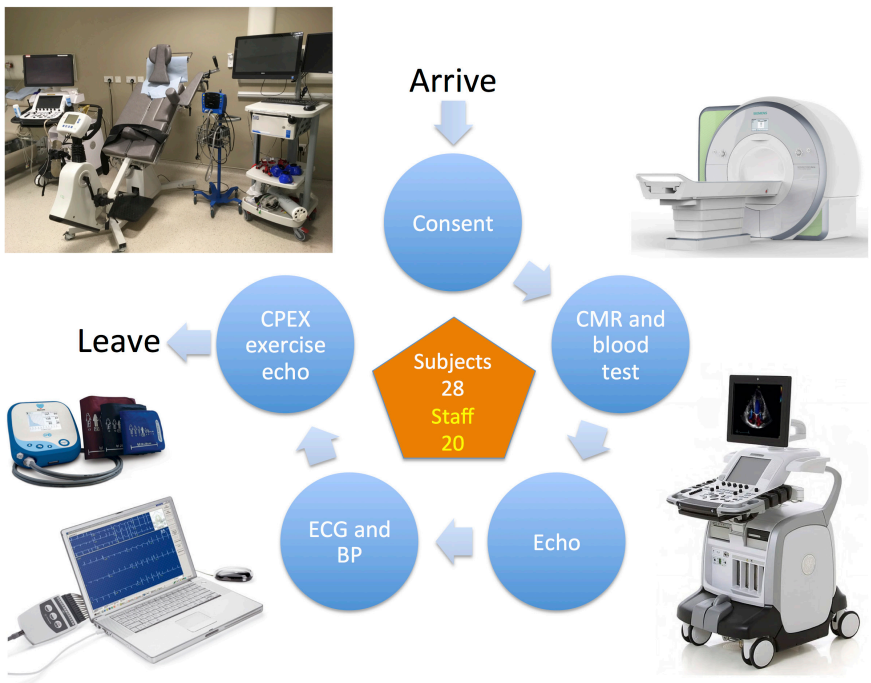

FIGURE 1 | The study visit testing circuit. BP, blood pressure; CMR, cardiac magnetic resonance; CPEX, cardiopulmonary exercise test; ECG, electrocardiogram.

Parametric Mapping for Myocardial Tissue Characterization: T1, T2, and ECV

Mid-ventricular short axis pre and post-contrast (15 min post 0.1 mmol/kg Dotarem) T1 maps were acquired by Modified Look-Locker Inversion recovery (MOLLI) sequence [pre: 5s(3s)3s, post: 4s(1s)3s(1s)2s]. MOLLI T1 maps with motion correction were used to generate automated extracellular volume (ECV) maps with contours in the mid-anteroseptum used for analysis, as previously described (Rosmini et al., 2018) based on the following equation:

$$ECV = [1 - Hct] \times \left(\frac{\Delta \left[1/T1myo \right]}{\Delta \left[1/T1blood \right]} \right)$$

Mid-ventricular short axis T2 maps were acquired with the mean segmental pixel value calculated from a region of interest drawn in the mid-anteroseptum.

Aortic Pulse Wave Velocity

Pulse wave velocity was measured with phase-contrast MR imaging. Phase-contrast sequences were acquired in the ascending aorta (at the level of the pulmonary bifurcation) and the descending thoracic aorta (at the level of the diaphragm) with a prospectively triggered, velocity encoded spoiled gradient echo sequence (flip angle = 20^o; pixel bandwidth = 457 Hz/pixel; uninterpolated resolution = 2.0 × 2.0 mm; acquisition matrix = 192 × 192; echo time = 2.46 ms; repetition time = 9.24 ms, slice thickness 6 mm; FOV: 380 × 380 mm, matrix: VENC: 150 cm/s). For assessment of the aortic arch length, an oblique-sagittal image of the aorta (candy cane view) was obtained using ECG-gated steady state free precession acquisition with breath hold. Calculation of flow wave transit time, aortic distance, and aortic pulse wave velocity was then undertaken as previously described (Bhuva et al., 2019, 2020).

Imaging Analysis

All resting imaging studies were analyzed by an accredited, experienced cardiologist (AD), blinded to subject identity and time point; 15 CMR studies were randomly selected and reanalyzed independently by another experienced cardiologist (AB or KM) for assessment of inter-observer variability. Exercise echocardiographic studies were analyzed by an accredited cardiac physiologist (JZ) and aortic pulse wave velocity was analyzed by two investigators (AB and NN).

Blood Samples

Non-fasting blood samples were collected into standard ethylenediaminetatraacetic acid (EDTA) and serum separating (SST) blood collection tubes during intravenous cannulation prior to CMR. On-site laboratory analysis included complete blood count, used to calculate the ECV and a renal chemistry sample, including creatinine and electrolytes. The remainder of whole blood and serum samples were saved in cryovials and stored at −80°C in refrigerators at St George's, University of London.

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing was performed using a semi-recumbent tilting cycle ergometer (Schiller ERG 911 BP/LS,

Schiller, Switzerland) with an incremental ramp protocol of 15–30 W/min, based on a pre-specified algorithm incorporating subject height and gender (**Supplementary Table S1**). Subjects were exercised to volitional exhaustion with continuous ECG monitoring. Maximal effort was assessed by the presence of a plateau in oxygen uptake seen in Wasserman Plot panel 3, respiratory exchange ratio (RER) > 1.15 and subject perceived exhaustion, as recognized parameters of assessment of effort (Society, 2003). Achievement of maximal predicted heart rate was a less reliable marker of maximal effort with testing conducted on a semi-recumbent cycle, as compared to a treadmill. Breath-by-breath pulmonary gas exchange and ventilation were continuously measured by metabolic cart (Quark CPET, COSMED, Rome, Italy), as previously described (Sharma et al., 2000). The ventilatory threshold was determined by the V-slope method, where two intersecting lines were drawn using dedicated software (Omnia, COSMED, Rome, Italy) on the VCO_2 vs VO_2 Wasserman Plot panel 5. Echocardiography was performed after 5 min exercise in the semi-recumbent position to assess augmentation in LV ejection fraction (EF) and stroke volume. To fully characterize exercise ability and potential using the semi-recumbent ergometer, both maximal (maximal VO_2 and percentage predicted maximal VO_2) and submaximal indices [oxygen uptake efficiency slope (OUES)] were assessed. In order to appropriately classify cardiorespiratory trainability by accounting for the random within-individual variation and measurement error, a combination of the technical error of measurement (TEM) and the minimal clinically important difference (MCID) were incorporated, as previously described (Williams et al., 2019). Studies were performed by four experienced cardiac physiologists working a rotational day schedule and analyzed by a single investigator (AD). Target exercise times were 5–12 min, if a subject at baseline exercised for more than 12 min to volitional exhaustion the ramp protocol was increased by 5 W/min on post marathon testing.

Statistical Analysis

Statistical analyses were performed with R version 3.3.0 (R Project for Statistical Computing). Project data were curated using REDCap data tools hosted at University College London (Harris et al., 2009). Data were tested for normality with the Shapiro–Wilk test and assessed in histograms. Normally distributed data are presented as mean ± standard deviation and skewed data are presented as median with inter-quartile range (IQR). Differences between baseline and post marathon time points were compared using a paired *t*-test, if parametric, or Wilcoxon signed rank test if non-parametric and expressed as mean difference. Differences in paired categorical data were compared using McNemar's test. Comparisons of two unpaired groups (likely responder and likely adverse responder) were assessed using a two-sample independent *t*-test. Comparisons of three unpaired groups (final cohort, injured, lost to follow up) were assessed by one-way ANOVA if continuous or by Chi-squared test if categorical. Reproducibility of measurements both between and within raters was assessed with two-way, mixed single measures intraclass correlation coefficient (ICC) analysis for absolute agreement. ICC > 0.75 = excellent, 0.6–0.74 = good, 0.4–0.59 = fair, and < 0.4 = poor, according to a previously published scale (Cicchetti, 1994). Statistical significance was defined as a two-tailed value of $P < 0.05$.

RESULTS

Study Cohort Demographics and Race Finishing Times

One hundred and twenty subjects were recruited into the study. Twenty-eight were lost to follow up as they only attended the baseline evaluation and did not return for follow up evaluation post marathon, predominantly due to scheduling difficulties in the required timeframe. Of these 28, 12 ran the London Marathon and 16 did not. All 28 were able to confirm that they were alive at the end of the study period and had suffered no clinical cardiac events. In addition, 24 were unable to complete their training due to musculoskeletal injury, they deferred their marathon places and despite not running the marathon they returned for repeat evaluation. These subjects reported continuing light exercise training once their injuries improved but were no longer adherent to a marathon running training plan. They were not included in the primary analysis but their results are appended separately in **Supplementary Table S2**. The final cohort of marathon completers consisted of 68 novice runners who underwent evaluations at study entry, 186 ± 4 days before the London Marathon in October 2015 and 16 ± 4 days after in May 2016 (**Figure 2**). Only the results from these marathon completers were included in the main analysis. One marathon completer omitted CMR on post marathon evaluation due to early pregnancy. Baseline measures are presented in **Table 1**. There was no difference in baseline characteristics between participants completing the study and those who were lost to follow up or injured. Subjects self-reported a median of 2.0 h of exercise per week (range 0–10 h, IQR 1.5–2.5 h) at the time of study entry.

The median race finishing time of the study cohort was 04:31:00 (HH:MM:SS, IQR: 04:08:30–05:02:00, range: 02:56:10–06:51:20). Median finishing times for men and women were 04:14:30 (IQR: 03:42:20–04:42:00) and 04:43:40 (IQR: 04:29:00–05:19:50), respectively. These are above the published median times for the 2016 London Marathon general race, which includes repeat marathon runners, at 04:04:23 for men and 04:39:27 for women (Mirror, 2016; Run247, 2018), though highly comparable (**Figure 3**).

Training Data

Thirty-eight subjects (32%) provided detailed training and detraining data recorded electronically on portable devices. The training activities of this sub-group are shown in **Figure 4** and **Supplementary Figures S1, S2**. The median training times fell below the recommended 17-week training plan, averaging 78% compliance when studied on a week-to-week basis (**Supplementary Table S3**).

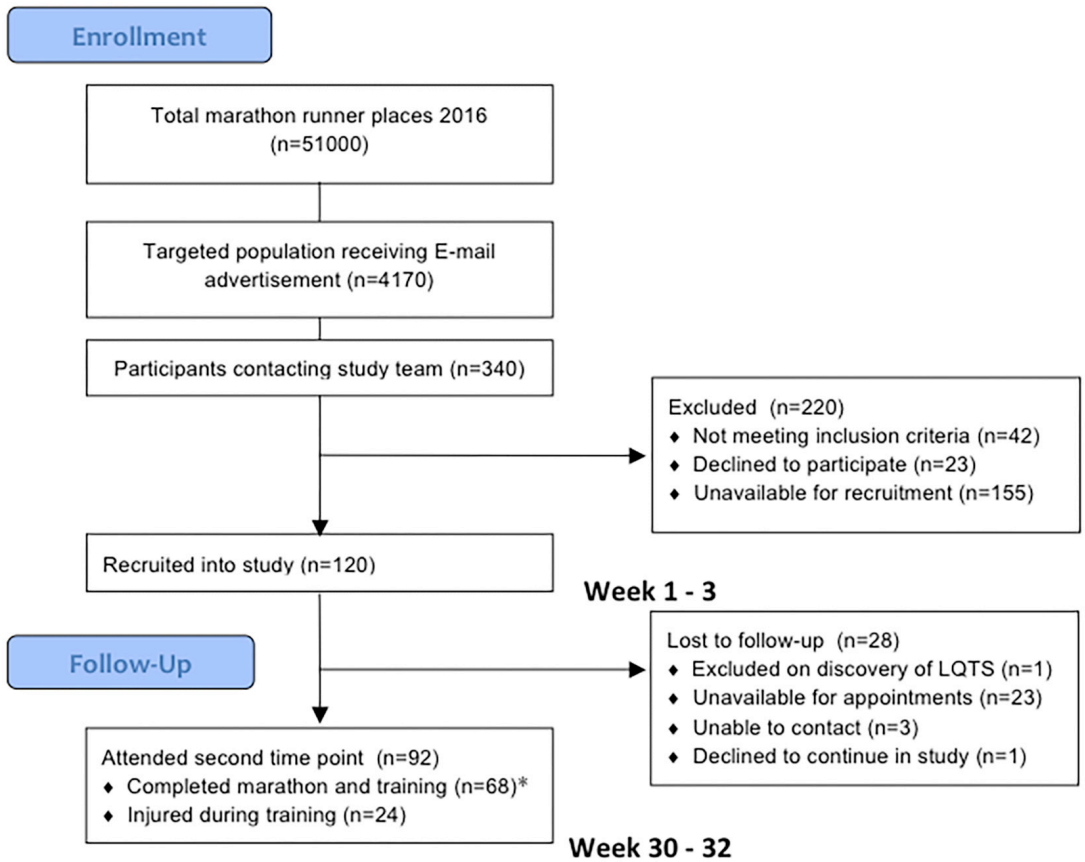

FIGURE 2 | Flow diagram of the trial profile. LQTS, long QT syndrome.

Cardiac Structure and Function

Structural and functional CMR measures of cardiac chambers are detailed in **Table 2** and **Supplementary Table S4**, demonstrating balanced eccentric remodeling and no change in LV or RV EF.

Cardiac remodeling changes were similar in both men and women, as detailed in **Table 3** and **Supplementary Table S5**. No changes were observed in echocardiographic diastolic function, myocardial strain, peak rotation, twist, or torsion parameters (**Supplementary Table S4**). LV stroke volume and EF at 5 min of exercise on cardiopulmonary exercise testing did not change after training. Limitations in image quality prevented accurate assessment of echocardiographic indices at peak exercise.

T1 and T2 values from multiparametric mapping did not change. A 1% reduction in ECV was matched by a 1% rise in blood hematocrit with no change in the myocardial partition coefficient, post-contrast T1 myocardial, or blood values. There was no evidence of LGE in any subject, including the additional 24 subjects who did not run the marathon due to injury but attended for re-evaluation.

Blood Pressure and Arterial Stiffness

Reductions were seen in the aortic pulse wave velocity (ascending to descending aorta), peripheral, and central BP. BP fell by 4/2 mmHg ($P < 0.01$) and aortic pulse wave velocity across the whole aorta fell by 0.2 m/s ($P = 0.02$). In sub-group analysis women, who were also noted to have lower baseline BP, experienced a greater BP reduction than men.

Cardiopulmonary Exercise Testing

Six (9%) of subjects at baseline exercised to volitional exhaustion in over 12 min, for whom the ramp protocol was increased by 5 W/min when returning for repeat evaluation post marathon. The remaining 62 subjects (91%) were tested on the same ramp protocol post marathon as the baseline exercise tests. Mean baseline exercise time was 09:38 ± 01:32 (MM:SS), which increased to 10:10 ± 01:42 post marathon ($P = 0.01$).

No changes were seen in maximal oxygen consumption (VO_2), as absolute values and percentage of predicted peak, OUES, or maximum metabolic equivalents achieved (METS), despite a mean increase in exercise time of 32 s and a median increase in peak power achieved of 15 W ($P < 0.01$). The ventilatory anaerobic threshold fell post marathon, both in absolute value and as a percentage of maximal VO_2.

Using the previously established coefficient of variation of 5.6% (Katch et al., 1982), the TEM was calculated by multiplying this value by the mean baseline peak VO_2, which was 37.91 ml/min/kg in this cohort, therefore TEM = 2.12 ml/kg/min. Applying previously defined criteria for MCID and peak VO_2

TABLE 1 | Baseline characteristics of study participants in the final cohort and comparison to subjects not completing training due to injury and lost to follow up.

	Final cohort completing marathon (n = 68)	Injured—unable to complete training (n = 24)	Lost to follow up (n = 28)	P-value
Age	29.5 ± 3.2	28.8 ± 3.3	27.9 ± 3.8	0.12
Male n(%)	36 (53)	10 (42)	14 (50)	0.64
Ethnicity (%)				0.64
White European	90	96	89	
Other	10	4	11	
Smoking status (%)				
Never smoker	82	83	71	0.65
Ex-smoker	12	8	21	
Current smoker	6	8	7	
Hours of exercise/week	2 [1.5, 2.5]	2 [1.5, 2.6]	2 [1.5, 3.1]	0.89
Weight (kg)	71.3 ± 12.5	72.7 ± 12.6	71.6 ± 14.7	0.74
BMI (kg/m^2)	23.4 ± 2.9	24.0 ± 3.1	24.4 ± 3.7	0.33
Peak VO_2 (ml/kg/min)	37.1 [32.8, 42.3]	37.2 [34.0, 40.5]	35.0 [30.4, 40.8]	0.39
Percentage predicted peak VO_2 (%)	106.7 ± 16.2	111.2 ± 14.9	102.7 ± 17.4	0.18
Systolic BP (mmHg)	119.6 ± 11.8	118.4 ± 11.5	121.8 ± 9.0	0.53
Diastolic BP (mmHg)	73.7 ± 5.3	74.5 ± 5.9	75.6 ± 5.7	0.29
Heart rate (bpm)	66.3 ± 13.8	68.8 ± 14.4	68.4 ± 14.9	0.69
iLV mass (g/m^2)	64.9 ± 12.1	63.4 ± 9.8	63.2 ± 11.6	0.76
iLV EDV (ml/m^2)	91.0 ± 14.3	90.0 ± 12.8	90.1 ± 12.0	0.93
iRV EDV (ml/m^2)	92.6 ± 14.3	93.0 ± 15.4	93.1 ± 13.7	0.99

Data expressed as mean ± SD if normally distributed. If non-normally distributed data expressed as median [IQR]. BMI, body mass index; BP, blood pressure; EDV, end-diastolic volume; iLV indexed to body surface area left ventricular; iRV, indexed to body surface area right ventricular; VO_2, oxygen consumption.

response (Williams et al., 2019), resulted in 7.6% likely adverse responders, 51.5% likely non-responders, 30.3% uncertain, and 10.6% likely responders in this population (**Figure 5**).

Those subjects who were likely responders based on the change in peak VO2 (n = 7) did not demonstrate differences in systolic function, cardiac dimensions, BP, or aortic pulse wave velocity compared with those subjects who were likely adverse responders (n = 5). Comparing the available mean weekly exercise volumes over the 17-week training period between likely responders (n = 4) with likely adverse responders (n = 3), there were no differences (**Supplementary Table S6**).

Electrocardiography

No changes were seen in resting heart rate, PR interval, QRS duration, corrected QT interval, or Sokolow–Lyon voltage (S in V_1 + R in V_5 or V_6, depending on the largest values). The prevalence of voltage criteria for ventricular hypertrophy and early repolarization pattern did not change (**Supplementary Table S4**).

Allometry, Body Composition, and Renal Function

There were no significant changes in weight, body mass index or percentage body fat over the study period. Serum creatinine decreased by 5 μmol/l ($P < 0.01$) post marathon.

Reproducibility of Measurements

Intra-observer and inter-observer agreement for all cardiac imaging measurements were excellent (**Supplementary Tables S7, S8**).

DISCUSSION

The aim of this study was to examine in detail the cardiovascular remodeling responses in real-world, young, novice marathon runners and explore any differences between men and women. There were a number of key study findings; first, that running a first marathon results in concentric biventricular remodeling that is more modest than previous longitudinal studies of marathon runners (Arbab-Zadeh et al., 2014; Zilinski et al., 2015). Second, a modest BP reduction was seen. Third, these changes occurred without an improvement in peak VO_2 and finally, responses were similar in men and women.

Blood Pressure and Renal Biochemistry

The reductions in peripheral and central BP demonstrated in this study were accompanied by a reduction in aortic pulse wave velocity, which is intriguing and suggests that a reduction in vascular stiffness may play a mechanistic role in normotensive, young exercising individuals. These findings have been reported previously in an extended cohort of this study, including older runners and finding greater regional distenibility in the descending aorta after marathon running (Bhuva et al., 2020). Though a 4/2 mmHg BP reduction seems small, this is highly consistent with the effect of exercise on BP reported in large meta-analyses, which is comparable with the effect of antihypertensive medication (Cornelissen and Smart, 2013; Naci et al., 2018) and also on aortic pulse wave velocity (Ashor et al., 2014). In terms of clinical relevance, if sustained, a 2 mmHg systolic BP reduction would be expected to reduce mortality from stroke by 10% and from vascular and ischemic heart disease by 7%, even in a low-risk, normotensive population (Lewington et al., 2002), underscoring the important role of increased physical activity in public health policy. It is recognized that age-matched, premenopausal women have lower BP than men (Maranon and Reckelhoff, 2013). In sub-group analysis women were noted to have a greater BP reduction post marathon than men, however, as we have limited information regarding important confounding factors such as training volume, intensity, lifestyle, and menstrual cycle stage, this finding should be interpreted with caution. Whether a favorable vascular remodeling response might contribute to the markedly lower incidence of sudden cardiac arrest during exercise in women (Marijon et al., 2011) merits further investigation.

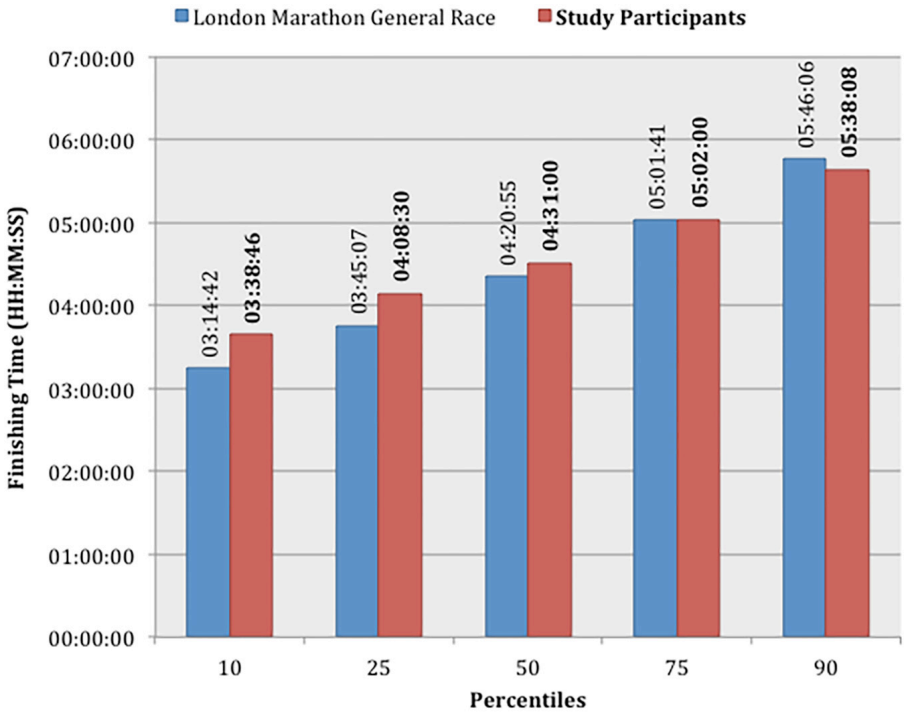

FIGURE 3 | Marathon race finishing times by fastest percentile of each cohort comparing study participants with the London Marathon General Race 2016.

A fall in serum creatinine is also an intriguing finding. Though marathon running has been associated with a substantial increase in serum creatinine and renal tubular injury on urine microscopy immediately afterward, this improves after 24 h (Mansour et al., 2017). Regular running training is associated with a fall in serum creatinine 2 weeks before a marathon race (Zilinski et al., 2015) and 2 weeks afterward, despite the acute rise on race day (Hewing et al., 2015). Future studies examining this dynamic relationship between exercise and renal function would be valuable, particularly including assessment of arterial wall mechanics and endothelial function.

Cardiac Structural Remodeling

We demonstrate a balanced, eccentric remodeling response, which is comparable between men and women. These changes are modest in comparison to previous, smaller studies involving running training in preparation for an endurance event with key differences in study populations and methodologies summarized in **Table 4**.

The intensity of peak training prior to the endurance event was greatest in the study by Arbab-Zadeh et al. (2014) where subjects trained for 7–9 h per week in the last 3 months of a year-long supervised program and demonstrated the greatest magnitude of cardiac remodeling and cardiorespiratory fitness response. Zilinski et al. (2015) training a larger population of older, male runners for 4 h per week achieving an average distance of 40 km per week, demonstrated smaller remodeling and cardiorespiratory fitness responses. Our study provided no supervised training intervention and observed in real-world novice marathon runners that cardiac remodeling is even more modest, without cardiorespiratory fitness improvement. This is consistent with a previously proposed schema that with increasing intensity and volume of training, subjects advance through a spectrum of increasing fitness and cardiac remodeling (Beaudry et al., 2016). The finding of a fall in ECV, though a recognized remodeling response in athletes (McDiarmid et al., 2016), is unlikely to represent a genuine change in myocardial structure as it was proportional to the rise in blood hematocrit, without any changes in the constituent myocardial or blood T1 mapping values pre or post contrast. The change in blood hematocrit is likely to be the result of seasonal variation and training effect, which has been previously described (Banfi et al., 2011).

This study found similar proportionate cardiac structural remodeling responses between men and women, who were advised to follow a 17-week beginner's training plan. A subsequent analysis of the study by Arbab-Zadeh et al. when comparing seven men to five women, found that despite exactly the same training, women experienced a blunting of cardiovascular response with peak VO_2, LV mass, and mean wall thickness plateauing after only 3 months of training, compared to months 9–12 in men (Howden et al., 2015). The likely reason for the differences observed in these studies relates to the differences in exercise volume, intensity, and duration. This suggests that there may be a dose–response relationship, where a threshold of exercise stimulus must be reached before differential responses in men and women are seen, which may be influenced by body

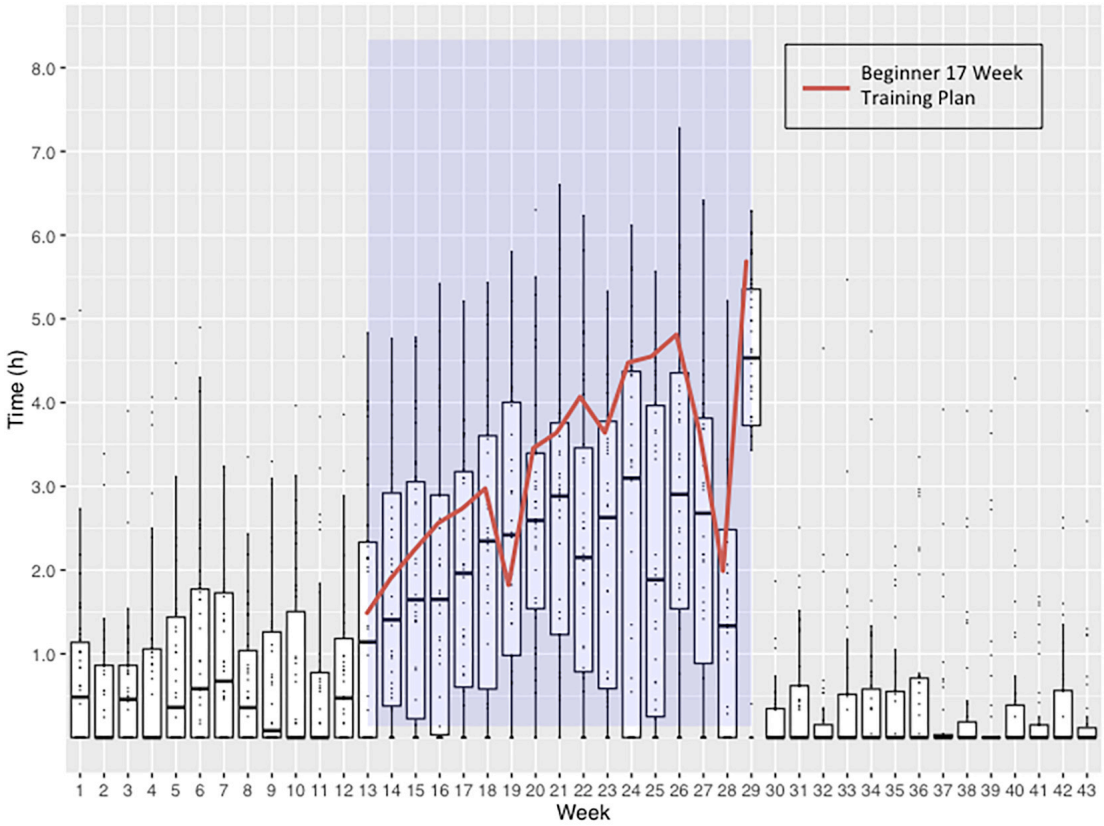

FIGURE 4 | Weekly time spent undertaking exercise by 38 subjects returning training logs. Blue shaded area represents the 17-Week Beginners Training Plan period. Boxplots represent the weekly distribution of time spent in exercise, highlighting the median and interquartile ranges. The Virgin Money London Marathon Beginner 17-Week Training Plan is overlaid to demonstrate the weekly exercise time targets the subjects should have been reaching. Week 17 includes the time spent running the marathon and achieving an average finishing time.

size, sex hormone profile, and hemodynamic response to exercise (Zemva and Rogel, 2001).

Cardiorespiratory Fitness

It was unexpected to find no difference in peak VO_2 and only 11% of runners demonstrating a likely cardiorespiratory training response. The observed fall in ventilatory threshold post-marathon, despite longer exercise time and higher peak power achieved may represent overreaching injury, which has previously been recognized in marathon runners (Kasikcioglu et al., 2008; Sierra et al., 2016). Based on the findings of the HERITAGE Family Study, which demonstrated a strong genetic determination of maximal VO_2, we had anticipated a potential increase of up to 16% in maximal VO_2, with wide variability in training response (Bouchard et al., 1999). The aforementioned studies of marathon runners showed a 4–18% increase in peak VO_2 (Arbab-Zadeh et al., 2014; Zilinski et al., 2015), where the training was supervised and exercise doses were greater than in our study. In addition to volume, intensity of training also affects cardiorespiratory fitness response, with several studies demonstrating superiority of high intensity interval training over moderate intensity continuous training (Wisløff et al., 2007; Milanović et al., 2015; Williams et al., 2019). Therefore, training administered by experienced coaches under supervision plays an important contribution to increasing peak VO_2, which real-world novice marathon runners following beginners training plans generally do not have. In addition, we did not observe changes in body fat, weight, or resting heart rate, which can be surrogate markers of athletic conditioning (Liou et al., 2016; Viana et al., 2019). Although we found no differences in cardiovascular remodeling or training volumes between likely cardiorespiratory responders and likely adverse responders, owing to the small number of subjects satisfying these definitions and fewer still recording training logs, there is a risk of type II statistical error, being unable to reject a false null hypothesis.

Despite an increase in peak VO_2 not being demonstrated in this study, a small substudy of this work previously reported that muscle VO_2, measured by near-infrared spectroscopy, increased by 48% after a first marathon run (Jones et al., 2017). Intriguingly, this suggests that adaptations in skeletal muscle improving metabolic capacity occur independently of peak VO_2 and when cardiovascular remodeling responses are modest. Future work exploring muscle arteriolar recruitment, perfusion, and their relationships with cardiovascular afterload and BP reduction

TABLE 2 | Cardiac imaging, hemodynamic, cardiorespiratory, and allometric measurements at baseline and post marathon.

	Baseline	Post marathon	*P*-value
Echocardiography			
iLV EDV (ml/m^2)	58.2 ± 12.2	62.5 ± 13.7	<0.01
iLV ESV (ml/m^2)	22.4 ± 5.9	26.0 ± 7.0	0.02
LV EF (%)	58.0 ± 4.7	58.5 ± 5.0	0.38
Exercise echocardiography			
5-min exercise LV EF (%)	69.0 ± 3.4	66.7 ± 9.1	0.70
5-min exercise iLV SV (ml/m^2)	81.4 ± 17.4	82.4 ± 19.6	0.20
CMR and hematocrit			
iLV EDV (ml/m^2)	91.2 ± 14.3	94.3 ± 14.8	<0.01
iLV ESV (ml/m^2)	33.3 ± 7.5	34.8 ± 8.2	0.02
LV EF (%)	63.5 ± 5.0	63.2 ± 5.5	0.71
iLV mass (g/m^2)	65.2 ± 11.9	68.1 ± 11.4	<0.01
Mean LV wall thickness (mm)	7.0 ± 0.9	7.1 ± 0.9	0.02
Native T1 (ms)	1011 ± 24	1009 ± 36	0.66
ECV (%)	26.8 ± 2.3	25.7 ± 2.4	<0.01
Hematocrit	0.42 ± 0.03	0.43 ± 0.04	<0.01
Native T2 (ms)	45.3 ± 3.5	45.5 ± 3.1	0.76
iRV EDV (ml/m^2)	92.8 ± 14.4	97.1 ± 16.0	<0.01
iRV ESV (ml/m^2)	40.5 ± 7.7	42.0 ± 9.1	0.01
RV EF (%)	56.7 ± 4.5	56.9 ± 4.4	0.71
CPET			
Peak VO_2 (ml/min/kg)	37.1 [32.8, 42.7]	37.5 [33.5, 42.0]	0.14
Percentage predicted peak VO_2 (%)	107.3 ± 16.1	109.6 ± 16.7	0.18
Ventilatory threshold as percentage of peak VO_2 (%)	61.4 ± 9.6	57.2 ± 8.6	<0.01
Exercise time (s)	578.2 ± 92.3	609.9 ± 101.7	0.01
Peak power (W)	200 [175, 265]	223 [195, 275]	<0.01
OUES (ml/min/L/min)	2686 [2327, 3373]	2582 [2228, 3211]	0.31
Peak HR (bt/min)	170.0 [162.0, 178.0]	171.0 [160.0, 187.0]	0.31
Peak HR percentage predicted (%)	88.67 ± 7.93	87.57 ± 6.26	0.37
Peak RER	1.21 ± 0.09	1.20 ± 0.09	0.67
Blood pressure and aortic PWV			
Systolic BP (mmHg)	120 ± 12	116 ± 12	<0.01
Diastolic BP (mmHg)	74 ± 5	72 ± 6	<0.01
CMR whole aorta PWV (m/s)	5.1 [4.8, 5.8]	4.9 [4.6, 5.6]	0.02
Allometry and renal function			
Body mass index	23.4 ± 2.9	23.5 ± 2.6	0.42
Body fat (%)	22.7 ± 7.8	22.5 ± 8.6	0.59
Creatinine (μmol/L)	74 ± 14	69 ± 13	<0.01

Data expressed as mean ± SD if normally distributed. If non-normally distributed data expressed as median [IQR]. BP, blood pressure; CMR, cardiac magnetic resonance; CPET, cardiopulmonary exercise test; ECV, extracellular volume; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; HR, heart rate; iLV indexed left ventricular; iRV, indexed right ventricular; LV, left ventricular; max, maximal; OUES, oxygen uptake efficiency slope; PWV, pulse wave velocity; RER, respiratory exchange ratio; RV, right ventricular; VO_2, oxygen consumption.

would be valuable to understand what influence exercise may have on these mechanisms.

Myocardial Injury

By evaluating runners 16 ± 4 days after the race, we could not reproduce evidence of ventricular dysfunction or myocardial edema found in previous studies (Neilan et al., 2006a; La Gerche et al., 2012; Gaudreault et al., 2013). These studies conducted tests immediately after (Neilan et al., 2006a; La Gerche et al., 2012) or within 2 days of race completion (Gaudreault et al., 2013). We intended to avoid immediate post-race evaluation due to the inherent differences in loading conditions, circulating catecholamines, sympathetic and vasomotor activation affecting outcomes of interest. If alterations in myocardial edema, strain, systolic or diastolic function occurred in the study participants, based on these previous studies, we would expect that they should normalize by the time of our assessment (Neilan et al., 2006b; La Gerche et al., 2012; Gaudreault et al., 2013).

As transient cardiac biomarker elevation has been shown to normalize by 36 h of race completion (Shave et al., 2007, 2010; Lippi et al., 2011; Scherr et al., 2011) and we found no clinical reason to suspect persistent elevation, such as myocardial fibrosis, we did not investigate this in our study.

Future research elucidating the biological mechanisms responsible for the beneficial effects of regular exercise, such as the reduction in arterial stiffness, may yield novel therapeutic strategies, ultimately aiming to harness the anti-atherosclerotic (Nocon et al., 2008), anti-obesity, anti-diabetic, anti-osteoporotic (Warburton et al., 2010), anti-cancer (Moore et al., 2016), antidepressant, and anti-dementia properties of physical activity (Hamer et al., 2014).

The chief strengths of the study were the careful and comprehensive phenotyping using state of the art cardiovascular imaging, balanced gender inclusion, and relatively large sample size for a longitudinal study of this nature with multiple tests conducted. The recruitment process, advertising to all potential subjects through the race organizers and the inclusion of all subjects regardless of adherence to a beginner's training plan allowed for the greatest generalizability, providing important real-world evidence on the effects of modest training on young, novice marathon runners and their cardiovascular health.

Limitations

Although inclusivity of undertrained marathon completers can be viewed as a strength of the study, it simultaneously represents a significant weakness as detailed training information was missing from the majority of subjects, which would have been valuable in examining undertraining and further associations between training volume or intensity and cardiovascular remodeling responses. Similarly, reductions to the final sample size through loss to follow up also impaired our ability to detect small changes with accuracy.

Treadmill cardiopulmonary exercise testing would have been the preferred method to assess cardiorespiratory fitness changes in marathon runners; however, we used semi-recumbent tilting cycle ergometers to facilitate dynamic assessment of

TABLE 3 | Cardiac imaging, hemodynamic, cardiorespiratory, and allometric measurements at baseline and post marathon, separated by gender.

	Baseline male subjects	Post marathon male subjects	Change	*P*-value	Baseline female subjects	Post marathon female subjects	Change	*P*-value
iLV EDV (ml/m^2)	98.1 ± 14.2	101.0 ± 14.7	2.9	0.02	83.2 ± 9.5	86.4 ± 10.6	3.2	<0.01
iLV ESV (ml/m^2)	36.2 ± 8.7	38.2 ± 8.7	2.0	<0.01	30.0 ± 3.7	30.7 ± 5.2	0.7	0.44
LV EF (%)	63.4 ± 5.2	62.3 ± 5.4	-1.0	0.20	63.7 ± 4.8	64.3 ± 5.6	0.6	0.59
iLV Mass (g/m^2)	72.9 ± 10.4	76.0 ± 8.7	3.1	<0.01	56.3 ± 5.4	59.0 ± 6.3	2.7	<0.01
Mean LV wall size (mm)	7.6 ± 0.7	7.7 ± 0.6	0.1	0.08	6.3 ± 0.6	6.4 ± 0.5	0.1	0.16
Native T1 (ms)	1001 ± 20.20	992.6 ± 30.46	-8	0.18	1023 ± 22.42	1028 ± 33.26	5	0.51
ECV (%)	25.3 ± 1.8	24.3 ± 1.7	-1.0	<0.01	28.3 ± 1.6	27.1 ± 2.3	-1.3	0.02
iRV EDV (ml/m^2)	100.2 ± 13.9	104.4 ± 15.5	4.2	0.02	84.2 ± 9.3	88.5 ± 12.0	4.3	<0.01
iRV ESV (ml/m^2)	43.9 ± 7.4	45.9 ± 9.1	2.0	0.05	36.0 ± 5.8	37.6 ± 6.8	1.5	0.11
RV EF (%)	56.2 ± 4.2	56.2 ± 4.5	0	0.98	57.2 ± 4.8	57.7 ± 4.1	0.5	0.63
CPET								
Peak VO_2 (ml/min/kg)	40.5 ± 6.8	42.6 ± 8.0	2.1	0.11	35.2 ± 4.5	35.3 ± 5.9	0.2	0.81
Percentage predicted Peak VO_2 (%)	99.7 ± 15.8	105 ± 18.0	5.3	0.11	115.2 ± 12.4	117.6 ± 15.1	2.4	0.37
Anaerobic threshold as percentage of Peak VO_2 (%)	59.6 ± 9.9	55.9 ± 8.4	-3.7	0.05	63.3 ± 9.1	58.6 ± 8.7	-4.7	0.07
Blood pressure and aortic PWV								
Systolic BP (mmHg)	124 ± 12	122 ± 11	-2	0.09	114 ± 10	109 ± 8	-5	<0.01
Diastolic BP (mmHg)	75 ± 5	73 ± 6	-2	0.13	73 ± 5	70 ± 5	-3	0.02
CMR whole aorta PWV (m/s)	5.4 ± 1.1	5.2 ± 0.8	-0.2	0.22	5.3 ± 1.0	4.9 ± 0.7	-0.4	0.08
Allometry and renal function								
BMI	24.1 ± 3.1	23.9 ± 2.6	-0.2	0.32	22.5 ± 2.4	23.0 ± 2.6	0.4	0.04
Body fat (%)	17.6 ± 5.6	16.4 ± 5.2	-1.2	0.01	28.4 ± 5.7	29.3 ± 6.2	0.9	0.06

Data expressed as mean ± SD if normally distributed. If non-normally distributed data expressed as median [IQR]. BP, blood pressure; CMR, cardiac magnetic resonance; CPET, cardiopulmonary exercise test; ECV, extracellular volume; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; iLV indexed left ventricular; iRV, indexed right ventricular; LV, left ventricular; max, maximal; METS, metabolic equivalent of task; OUES, oxygen uptake efficiency slope; PWV, pulse wave velocity; RV, right ventricular; VO_2, oxygen consumption.

cardiac function and peripheral blood flow (Jones et al., 2017). As the post marathon cardiopulmonary exercise test took place after 7–21 days of detraining, peak VO_2 and ventilatory threshold values may have declined from peak performance levels by variable amounts. In addition, subjects who did not achieve the recommended preparatory training may have suffered a reduction in performance after running the marathon resulting from an overreaching syndrome (Kasikcioglu et al., 2008). These limitations may have been addressed by additional assessments at interim time points during training, which would have the potential to enhance our understanding of phasic cardiac remodeling (Arbab-Zadeh et al., 2014; Weiner et al., 2015) and peak VO_2 dynamics pre and post race.

This study did not include a control group, instead each subject acted as their own control investigating the association between training as a transient exposure and cardiovascular remodeling as an outcome. Therefore, the changes observed may have resulted from confounding factors, such as seasonal differences between October 2015 (baseline) and May 2016 (post marathon), rather than a causal effect of exercise training. BP is susceptible to seasonal differences (Alpérovitch et al., 2009), with 35 years olds experiencing a 2/2 mmHg lower BP on a warm summer day compared to a cold winter day (Brennan et al., 1982). A proposed mechanistic explanation suggests that longer daytime length and higher vitamin D levels may be responsible for a small BP reduction (Witham et al., 2009); however, exposure to sunlight is a challenging variable to control for between exercisers and sedentary controls. Though we were able to record that nine women (28%) were using combined oral contraception, one woman was using the progesterone-only pill (3%) and one woman had a levonorgestrel-releasing intrauterine system (3%) during the study, we did not obtain information regarding menstrual cycle stage at the time of testing. Oral contraceptive use can be associated with increases in BP and stages of the menstrual cycle can affect baroreflex control of sympathetic activity (Joyner et al., 2016). We were not able to evaluate these interactions in this study, which may have confounded the results.

With respect to harm in endurance running, this study was not designed to address rare but clinically important events such as sudden cardiac arrest or its causes. The majority of sports-related sudden cardiac arrests in the general population occur in men over 35 years of age with occult atherosclerotic coronary disease (Marijon et al., 2011, 2015), who were not included in this study. Future studies investigating the causes of sudden cardiac arrest during mass participation events will require a national registry with mandatory reporting (Maron et al., 2009) combined with systematic clinical investigation of victims and potentially including their families where no cause is found (Behr et al., 2008; Papadakis et al., 2013, 2018; Basso et al., 2017; Lahrouchi et al., 2017).

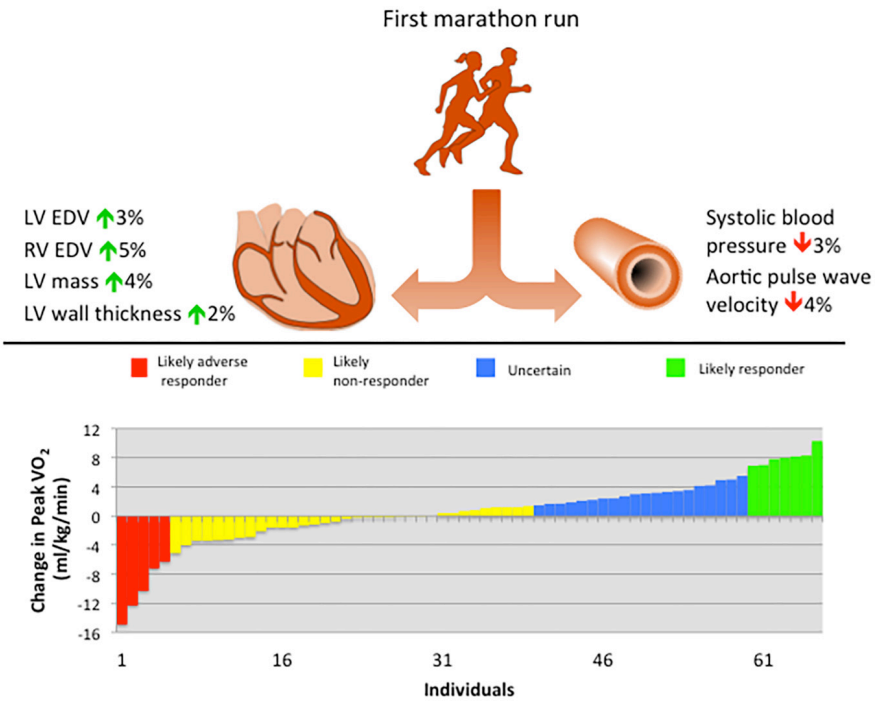

FIGURE 5 | Summary of principal findings of cardiovascular remodeling following training for a first marathon run, including waterfall plot of cardiorespiratory fitness response. EDV, end-diastolic volume; LV, left ventricular; RV, right ventricular; VO_2, oxygen consumption.

TABLE 4 | Comparative summary of longitudinal cardiac remodeling studies in marathon runners including preparatory training.

Study	Year	Subjects, *n*	Mean age (y)	Female (%)	Exercise exposure	Imaging modality	Peak exercise (h/week)	Increase in peak VO_2 (%)	Summary
Arbab-Zadeh et al. Circulation	2014	12	29	42	Running for 1 year—supervised	CMR	7–9	17.6	Increased LV mass by 21%, LVEDV by 18%, LV wall thickness by 16%, RV mass by 30%, and RVEDV by 27%. Early concentric LV remodeling then later eccentric remodeling response. RV remodeling was eccentric throughout
Zilinski et al. Circ cardiovasc imaging	2015	45	48	0	Running for 18 weeks—supervised	Echo	4	3.8	Increased LV mass by 14%, LVEDV by 10%, LV wall thickness by 5%, LV length by 5%, RVEDA by 6%, and LAEDV by 11%. Enhanced LV diastolic function
Present study		68	30	47	Running for 17 weeks—unsupervised	Echo CMR	2.7–3.9*	NS	Increased LV mass by 4%, LVEDV by 3%, LV wall thickness by 2%, and RVEDV by 5%. Modest eccentric biventricular remodeling. BP reduced by 4/2 mmHg and aortic PWV by 4%

*CMR, cardiac magnetic resonance; Echo; echocardiography; LAEDV, left atrial end-diastolic volume; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; NS, not significant; RVEDA, right ventricular end-diastolic area; RVEDV, right ventricular end-diastolic volume. *2.7 h/week was the median training time over the 8 weeks prior to the race, recorded from 32% of the study cohort. 3.9 h/week was the median training time over the final 8 weeks of the recommended beginner's training plan, which the study participants were encouraged to follow.*

CONCLUSION

Despite ongoing concerns regarding the cardiovascular safety of marathon running, this study demonstrates a reduction in BP and vascular stiffness in real-world, young, normotensive men and women. These benefits come despite more modest cardiovascular remodeling and cardiorespiratory fitness responses than previously reported in studies involving supervised training. We found no evidence of myocardial injury in first time marathon runners achieving an average finishing time. In clinical practice, real-world evidence of the effects of typical marathon training on cardiovascular health provides important information for the public and medical profession about an increasingly popular mass participation event.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the National Research Ethics Service; Queen Square, London committee granted ethical approval (15/LO/086). The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AD drafted the manuscript, contributed to the conception and design of the work, and contributed to the acquisition, analysis, or interpretation of data for the work. JM and SS contributed to the conception or design of the work and critically revised the manuscript. AB, JZ, RB, AA-G, SJ, NN, KM, YY, JA, TT, SR, MR, PS, JW, and DC contributed to the acquisition, analysis, or interpretation of data for the work. CT, GF, EP, HD, IC, AH, RS, CM, and GL critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2020.00232/full#supplementary-material

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SCIENTIFIC ARTICLE

Prevalence of abnormal findings in 230 knees of asymptomatic adults using 3.0 T MRI

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Abstract

Objective To identify abnormalities in asymptomatic sedentary individuals using 3.0 Tesla high-resolution MRI.

Materials and methods The cohort comprised of 230 knees of 115 uninjured sedentary adults (51 males, 64 females; median age: 44 years). All participants had bilateral knee 3.0 T MRIs. Two senior musculoskeletal radiologists graded all intraarticular knee structures using validated scoring systems. Participants completed Knee Injury and Osteoarthritis Outcome Score questionnaires at the time of the MRI scan.

Results MRI showed abnormalities in the majority (97%) of knees. Thirty percent knees had meniscal tears: horizontal (23%), complex (3%), vertical (2%), radial (2%) and bucket handle (1%). Cartilage and bone marrow abnormalities were prevalent at the patellofemoral joint (57% knees and 48% knees, respectively). Moderate and severe cartilage lesions were common, in 19% and 31% knees, respectively, while moderate and severe bone marrow oedema in 19% and 31% knees, respectively. Moderate-intensity lesion in tendons was found in 21% knees and high-grade tendonitis in 6% knees—the patellar (11% and 2%, respectively) and quadriceps (7% and 2%, respectively) tendons being most affected. Three percent partial ligamentous ruptures were found, especially of the anterior cruciate ligament (2%).

Conclusion Nearly all knees of asymptomatic adults showed abnormalities in at least one knee structure on MRI. Meniscal tears, cartilage and bone marrow lesions of the patellofemoral joint were the most common pathological findings. Bucket handle and complex meniscal tears were reported for the first time in asymptomatic knees.

Keywords Knee injuries · Pain-free · Radiology · Elderly

Introduction

Pathologies of the knee joint increase with age, and may be already existing on magnetic resonance imaging (MRI) before middle age, even without symptoms [1].

In fact, both well and poorly functioning knees can have similar damage, making it difficult to correlate relevant MRI findings with the patients' knee pain [2–4]. Advice on permitted load and stress limits in asymptomatic knee pathologies to prevent from advancing osteoarthritis (OA) remain unclear [1].

MRI has high sensitivity for the detection of subtle changes of joint structures [5, 6]. The estimated prevalence of MRI lesions in asymptomatic knees varies significantly between studies, from 0 to 75% [2, 3]. This is due to varying study designs, including different MRI field strengths and sequences employed—indicative of variation in diagnostic accuracy [7, 8]—as well as cohorts of varying size and levels of physical activity [1].

Although 1.5 T MRI is widely clinically used, limitations have been acknowledged, particularly in evaluating

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abnormalities of the hyaline articular cartilage and meniscus [9–11]. Existing literature demonstrates that 3.0 T MRI provides important clinical benefits over 1.5 T, as the stronger field strength increases signal-to-noise ratio allowing improved visualisation of anatomical and pathological structures [5, 12]. Additionally, using a multichannel coil improves sensitivity and diagnostic quality [13, 14].

The purpose of this study was to determine the prevalence of abnormal knee findings in asymptomatic adults by means of a high-field strength 3.0 Tesla (T) MRI and multichannel knee coil. This is the largest study to date using this high-resolution technology to provide a robust analysis of all knee structures.

Methods

Study design and participants

This was a prospective cohort study including asymptomatic adults. The study received ethical approval and all volunteers provided written informed consent before participation.

We recruited 115 asymptomatic volunteers (51 males, 64 females; median age: 44 years, range 25–73 years). The study was London-based and the volunteers were 95% Welsh/English/Scottish/Northern Irish/British, of white ethnicity. Twenty-five volunteers were aged < 40 years and 90 were aged ≥ 40 years. The median body mass index (BMI) was 25 (19.6–38.1) kg/m^2 and physical activity of low intensity was 2 (0–4) h/week. The main inclusion criteria were sedentary individuals, not meeting physical activity requirements of 30 min of moderate-intensity physical activity, 5 days/week, or 20 min of more intense physical activities, 3 days/week, based on existing health recommendations [15–17]; no present or previous history of knee injury; no prior knee surgery and asymptomatic knee joints. Pregnant women, individuals aged < 18 years, non-sedentary, with known knee problems or poor cardiovascular health were excluded from the study.

The participants were asked to complete a questionnaire called The Knee Injury and Osteoarthritis Outcome Score (KOOS) to assess their perceived knee condition and ensure that they were asymptomatic [18].

MRI protocol

All volunteers underwent bilateral knee 3 Tesla MR (Prisma, Siemens Healthcare, Erlangen, Germany) with a dedicated 15-channel knee coil. The imaging protocol included 3 proton density–weighted fat-suppressed (PD FS) sequences in axial (repetition time/echo time [ms]: 4630/37), sagittal (4200/41) and coronal planes (5240/41). All slices were 3 mm thick, with an image size/acquisition matrix of 320 × 320 pixels. The scanning time per volunteer was 25 min in total (to scan both knees of each volunteer).

Imaging analysis

All MR images were reviewed using a picture archiving and communications system (PACS) workstation by a senior musculoskeletal radiologist with 10-years' experience at consultant level. Twenty percent of the cohort were randomly selected for an additional independent evaluation by a second musculoskeletal radiologist with 9-years' experience at a consultant level.

In case of discrepancies between the radiologists' reports concerning the findings, agreement (consensus scores) was achieved by radiologists with a consensus reading in a second MRI reporting session.

MRI findings of the knee joint were analysed using different validated scoring systems for the presence of any signal changes/lesions of varying severity for the following structures: menisci, cartilage, bone marrow, tendons, ligaments (Table 1) [3, 19–24]. Other findings were also specified, including effusion, synovial collections (prepatellar bursitis, pes anserine bursitis, Hoffa's synovitis) and cysts (Baker's cyst, other ganglion cysts; Table 1) [25, 26]. The scoring systems are summarised in Appendix 1 (Supplementary Materials). The patella was divided anatomically into medial and lateral regions, with the ridge being considered as part of the medial region. The tibia was divided into medial and lateral regions. The femur was divided into medial, lateral and trochlea regions and the trochlea was further divided into medial, central and lateral. The medial and lateral menisci were each divided into subregions: anterior horn and posterior horn. Scores were assigned for each individual region. All MRI abnormalities with a grade/score > 0 were counted.

Table 1 Grading systems for all assessed knee features on MRI

Knee feature	Grading system
Meniscus	Modified BLOKS [19] and ACLOAS [20]†
Cartilage	Modified Noyes and Stabler [3, 21, 22]††
Bone marrow	KOSS [23]
Tendons	Johnson DP et al. [24]†††
Ligaments	ACLOAS [20]
Joint effusion	WORMS [25]
Synovial collections*	Binary—MOAKS [26]
Iliotibial band	Binary—MOAKS [26]
Cysts**	Binary

BLOKS, Boston Leeds Osteoarthritis Knee Score; *ACLOAS*, Anterior Cruciate Ligament OsteoArthritis; *KOSS*, Knee Osteoarthritis Scoring System; *WORMS*, Whole-Organ Magnetic Resonance Imaging Score; *MOAKS*, MRI Osteoarthritis Knee Score. *Synovial collections: prepatellar bursitis, pes anserine bursitis, Hoffa's synovitis; **cysts: Baker's cyst, other ganglion cysts. † Both horns of the meniscus were assessed, except for the body. †† A modified Noyes system on a scale 0–4 used by several papers was included here. ††† Scoring system primarily designed for the patellar tendon and was adjusted to include other tendons. Binary scoring system was defined as present/absent

Statistical analysis

Comparisons between groups were performed using the unpaired *t* test, Mann–Whitney *U* test or chi-squared test respectively. Possible associations were explored by calculating odds ratios (OR) with 95% confidence intervals (CI). Statistical significance was defined as $p < 0.05$ (GraphPad Prism, version 6.0c).

Results

Nearly all knees (227/230; [97%]) of asymptomatic individuals showed abnormalities in at least one of the knee structures on MRI, of varying grades of severity. These findings included meniscal tears, cartilage abnormalities, bone marrow oedema and tendon and ligament abnormalities. No major discrepancies between the scores of the two radiologists were reported. Mean KOOS scores for each individual item were ≥ 90/100: symptoms (90.0 ± 14.0); pain (94.9 ± 8.8); function in daily living (97.1 ± 6.5); function in sport and recreation (92.3 ± 11.6) and knee-related quality of life (90.4 ± 13.8). Further details are presented in Appendices 2 and 3 (Supplementary Materials).

Meniscal tears: prevalence, location, type

The prevalence of asymptomatic meniscal tears was 30% in knees (Table 2). Meniscal degeneration was present in a further 18%.

The majority of tears were located in the medial meniscus (93%), and in its posterior horn (91%; Table 2). Lateral meniscal tears were equally found in both the posterior and anterior horns.

The types of meniscal tears that we found were horizontal (23% knees), complex (3%), vertical (2%), radial (2%) and bucket handle tears (1%); meniscal extrusion was present in 3% knees (Table 2, Fig. 1).

Articular cartilage abnormalities: prevalence, severity, location

Cartilage abnormalities were present in 62% of the scanned knees (Table 3). The severity of cartilage defects were as follows: 20% knees had minor grade 1 cartilage lesions, 19% knees had grade 2, 19% knees grade 3 (moderate) cartilage lesions, 31% knees grade 4 (severe) cartilage lesions (Fig. 2); 41% knees had grade 3 and/or 4 lesions (moderate/severe).

The patellofemoral compartment was the most affected region (57% knees).

Bone marrow oedema: prevalence, severity, location

Bone marrow oedema–like lesions were found in 52% of the scanned knees (Table 3). By looking at levels of severity, 18% knees had only minor grade 1 bone marrow oedema lesions, 25% knees had grade 2 (moderate) oedema lesions, 7% knees had grade 3 (severe) lesions (Fig. 2) and 27% knees had grade 2 and/or 3 lesions (moderate/severe).

The region presenting with the majority of MRI changes was the patellofemoral compartment (43% knees).

Tendon abnormalities: prevalence, severity, location

We identified 46% knees with tendon abnormalities (Table 4). In terms of levels of severity, 22% knees had only minor increased signal intensity (grade 1), 21% knees had grade 2 moderate signal intensity lesions and 6% knees had grade 3 lesions/high-grade tendonitis (Fig. 3). MRI signal changes were most visible in the patellar tendon (27% knees), followed by the quadriceps tendon (13% knees).

Ligamentous abnormalities: prevalence, severity, location

We found 38% knees (Table 4) with ligamentous abnormalities. In terms of levels of severity, 35% knees had only a thickened ligament (grade 1) and 3% knees had grade 2/partial rupture. No grade 3 injuries were identified.

The anterior cruciate ligament was the most affected ligament among the participants (34% knees), with the other ligaments presenting only very few lesions (Table 4).

Prevalence of other findings

Joint effusion was found in 3% knees: grade 2 ($n = 7$) and grade 3 ($n = 1$).

Other findings included Baker's cyst (33% knees), prepatellar bursitis (26% knees), Hoffa's synovitis (23% knees), other ganglion cysts (20% knees) and pes anserine bursitis (6% knees).

Associations between lesions

There was an association between the presence of abnormal cartilage signal and bone marrow oedema in knees ($p < 0.0001$). Participants with cartilage abnormalities were 8.0 times more likely to have bone marrow oedema lesion (95% CI, 1.6–10.3; $p = 0.0023$). No associations were found for other lesions ($p > 0.005$; Appendix 4 (Supplementary Materials)).

Participant characteristics

No difference in the prevalence of MRI abnormalities between males and females was found.

The prevalence of lesions generally increased with age. The mean age for the participants with a meniscal tear was slightly higher than those without a tear (47.5 ± 9.9 years ($n = 50$) vs 42.6 ± 7.0 ($n = 65$); $p = p = 0.0027$, unpaired *t* test). The mean age for those with bone marrow oedema was slightly higher than those without oedema (46.4 ± 8.9 years ($n = 72$) vs 42.0 ± 7.8

Table 2 Prevalence of meniscal tears and degeneration in 230 asymptomatic knees

Meniscal anatomy		Number (%) of knees with meniscal abnormalities*								
		Meniscal degeneration	Meniscal extrusion	Meniscal tears						
				Horizontal	Vertical	Radial	Root	Bucket handle	Complex	Any type of tear (at least 1)
Medial	AH	2 (1%)	0 (0%)	6 (3%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	7 (3%)
	PH	37 (16%)	5(2%)	53 (23%)	5 (2%)	5 (2%)	0 (0%)	2 (1%)	5 (2%)	70 (30%)
Lateral	AH	3 (1%)	0 (0%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	3 (1%)
	PH	5 (2%)	1 (0.4%)	2 (1%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (1%)
Any location		41 (18%)	6 (3%)	53 (23%)	5 (2%)	5 (2%)	0 (0%)	2 (1%)	6 (3%)	70 (30%)

*Grades were defined according to modified BLOKS [19] and ACLOAS [20] systems; *BLOKS*, Boston Leeds Osteoarthritis Knee Score; *ACLOAS*, Anterior Cruciate Ligament OsteoArthritis; *AH*, anterior horn; *PH*, posterior meniscal horn. The percentages do not all add up to 100% because each knee could have more than one type of meniscal abnormality and in more than one segment of the meniscus

($n = 43$); $p = p = 0.0071$, unpaired t test). Participants aged ≥ 40 years old were 4.0 times more likely to have abnormal cartilage signal (95% CI, 1.6–10.3; $p = 0.0023$). In terms of level of severity, 51 of 90 participants (57%) aged ≥ 40 years had high grade 3 or 4 cartilage lesions. And 10 of 25 participants (40%) aged < 40 had grade 3 or 4 cartilage lesion. The difference was not statistically significant ($p = 0.140$, chi-squared). The distribution of prevalences per knees is available in Table 5.

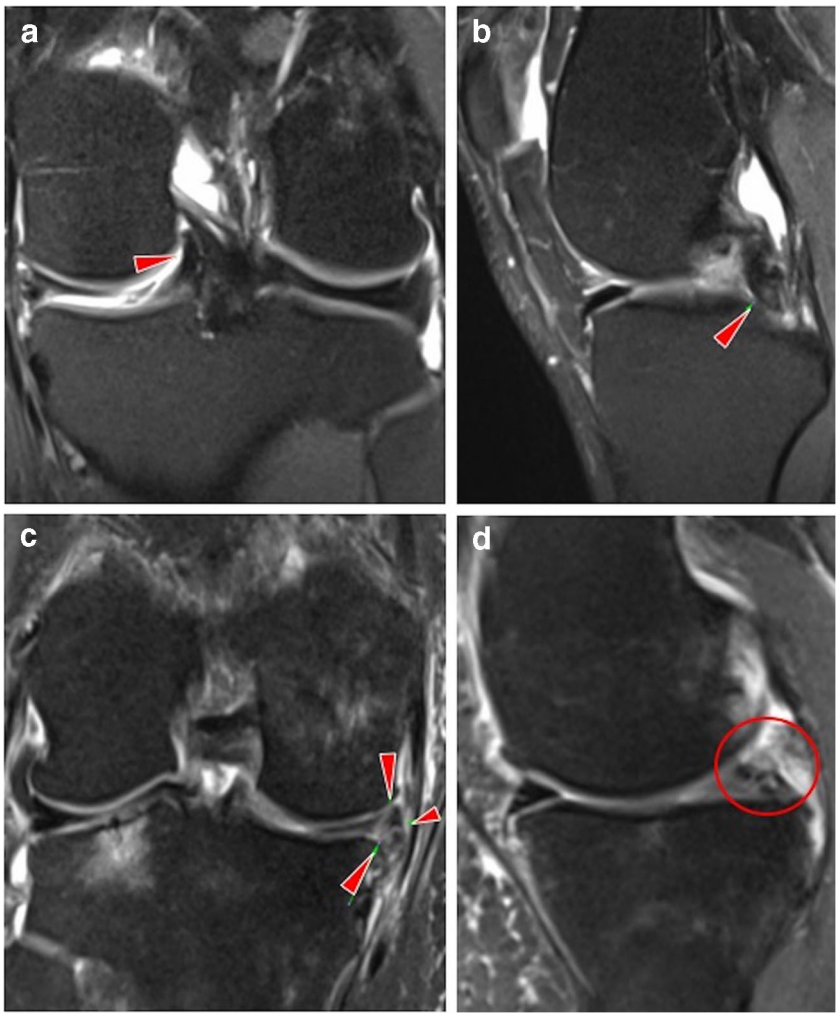

Fig. 1 Coronal proton-density fat-saturated MR images (a, c) and sagittal images (b, d) demonstrate bucket handle tear (a, b; arrowheads) in the left knee of a 54-year-old man, and complex macerated (c, arrowheads; d, circle) meniscal tear in the right knee of a 57-year-old woman

Table 3 Prevalence of MRI abnormalities of the articular cartilage and bone marrow in 230 asymptomatic knees

Anatomical structure	Number (%) of knees graded per structure*					
	0	1	2	3	4	Any grade ≥ 1
Cartilage						
Patellofemoral	100 (43%)	37 (16%)	32 (14%)	28 (12%)	57 (25%)	130 (57%)
Medial tibiofemoral	190 (83%)	11 (5%)	9 (4%)	6 (3%)	14 (6%)	40 (17%)
Lateral tibiofemoral	207 (90%)	9 (4%)	2 (1%)	4 (2%)	10 (4%)	23 (10%)
Any knee compartment**	87 (38%)	46 (20%)	43 (19%)	43 (19%)	71 (31%)	143 (62%)
Bone marrow						
Patellofemoral	132 (57%)	24 (10%)	39 (17%)	11 (5%)	-	98 (43%)
Medial tibiofemoral	200 (87%)	13 (6%)	14 (6%)	5 (2%)	-	30 (13%)
Lateral tibiofemoral	215 (93%)	5 (2%)	9 (4%)	2 (1%)	-	15 (7%)
Any knee compartment**	111 (48%)	42 (18%)	57 (25%)	16 (7%)	-	119 (52%)

*Grades were defined according to a modified Noyes system [3, 21, 22] for cartilage lesions and *KOSS*, Knee Osteoarthritis Scoring System [23], for bone marrow oedema; **any abnormalities in any of the knee joints. The percentages do not add up to 100% because each knee could have more than one type/grade of lesion, in more than one location. All knees with any type of lesion 1–4 were counted separately to avoid counting the same knees more than once

The BMI of participants with MRI abnormalities was not significantly different from those without abnormalities, except for tendon abnormalities ($p = 0.0002$). The odds of a participant with BMI ≥ 25 kg/m^2 (overweight) presenting with a tendon abnormality were 3.3 (95% CI, 1.5–7.6). A total of 28 of 60 participants (47%) with BMI ≥ 25 kg/m^2 had grade 2 or 3 high-intensity tendonitis (Fig. 3); 18 of 55 participants (33%) with BMI < 25 kg/m^2 showed high-grade tendon lesion (the difference was not statistically significant, $p = 0.128$, chi-squared).

Discussion

Overall our study showed a high prevalence of 3.0 T MRI pathologies in the knees of asymptomatic adults: meniscal tears, including few complex and bucket handle tears; patellofemoral cartilage lesions and bone marrow oedema lesions of moderate to severe grade. The prevalences were higher than in previous studies. The KOOS results confirmed that the participants had no perceived knee problems/symptoms of functional limitation, despite the observed lesions on MRI.

Previous studies in asymptomatic uninjured knees

A number of studies have reported prevalences of knee abnormalities in uninjured asymptomatic individuals. Culvenor et al. [1] collated in a recent systematic review the pooled results from the existing evidence.

The first interesting finding is the prevalence of meniscal tears. While 44 studies (3761 knees from 2817 participants) reported prevalence of meniscal tears with an overall pooled

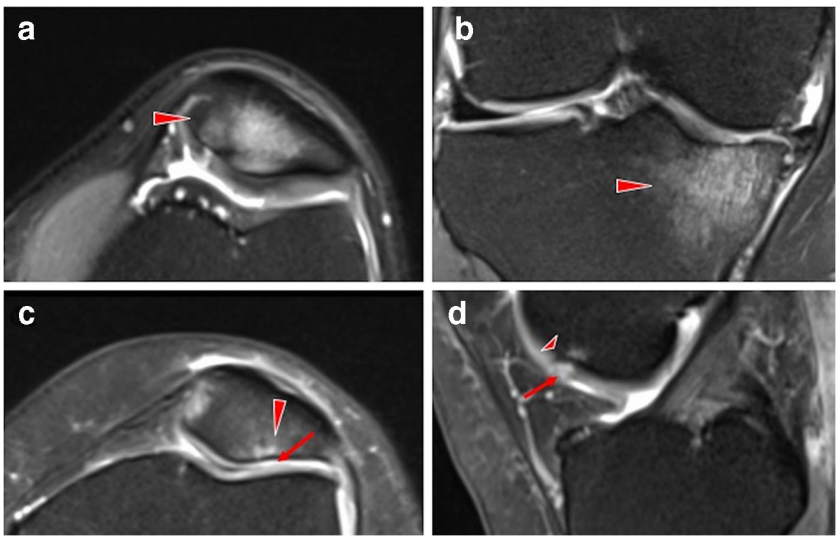

Fig. 2 Axial proton-density fat-saturated MR images (a, c), coronal (b) and sagittal images (d) of high-grade bone marrow oedema lesion (grade 3: diameter ≥ 20 mm; in the (a) patella of the left knee of a 40-year-old man, (b) tibia of the right knee of a 59-year-old man; arrowheads) and high-grade cartilage defect (grade 4: full thickness defect exposing the bone; in the (c) patella of the left knee of a 44-year-old woman; arrow; with subchondral bone marrow oedema, arrowhead; (d) femur of the right knee of a 31-year-old woman; arrow; with subchondral ganglion cyst; small arrowhead)

Table 4 Prevalence of MRI abnormalities of the knee tendons and ligaments of 230 asymptomatic knees

Anatomical structure	Number (%) of knees graded per structure*				
	0	1	2	3	Any grade ≥ 1
Tendons					
Patellar	169 (73%)	30 (13%)	26 (11%)	5 (2%)	61 (27%)
Quadriceps	201 (87%)	9 (4%)	16 (7%)	4 (2%)	29 (13%)
Semimembranosus	207 (90%)	11 (5%)	9 (4%)	3 (1%)	23 (10%)
Sartorius	228 (99%)	1 (0.4%)	0 (0%)	1 (0.4%)	2 (1%)
Gracilis	222 (97%)	4 (2%)	0 (0%)	4 (2%)	8 (3%)
Any tendon	124 (54%)	51 (22%)	48 (21%)	14 (6%)	106 (46%)
Ligaments					
Anterior cruciate	151 (66%)	75 (33%)	4 (2%)	0 (0%)	79 (34%)
Posterior cruciate	228 (99%)	1 (0.4%)	1 (0.4%)	0 (0%)	2 (1%)
Medial collateral	224 (97%)	4 (2%)	2 (1%)	0 (0%)	6 (3%)
Lateral collateral	227 (99%)	3 (1%)	0 (0%)	0 (0%)	3 (1%)
Any ligament	143 (62%)	81 (35%)	7 (3%)	0 (0%)	87 (38%)

*Grades were defined according to Johnson DP et al. [24] for tendon abnormalities and *ACLOAS*, Anterior Cruciate Ligament Osteoarthritis Score [20], for ligamentous abnormalities. The percentages do not add up to 100% because each knee could have more than one type/grade of lesion, in more than one location. All knees with any type of lesion 1–3 were counted separately to avoid counting the same knees more than once

prevalence estimate of 10% (95% CI 7 to 13%; $I^2 = 87.2\%$) [1], we hereby reported a significantly higher prevalence of 30%. Moreover, we identified vertical, radial, bucket handle and complex tears which are not common in asymptomatic individuals [27]. Therefore, they may be clinically more meaningful.

In terms of cartilage defects (partial and full thickness), 42 studies (4322 knees from 3446 participants) reported an overall pooled prevalence estimate of 24% (95% CI 15 to 34%; $I^2 = 97.8\%$) [1]. Our study however showed a higher prevalence that exceeds this interval: 41% cartilage defects of moderate to severe damage, with grade 4 lesions being most prevalent in asymptomatic adults (31% knees). The clinical significance of this is uncertain, raising questions about the factors leading to cartilage damage and what mechanisms of pathology prevention could be employed.

Thirty-four studies (4089 knees from 3255 participants) reported bone marrow lesions prevalence with an overall pooled prevalence estimate of 18% (95% CI 12 to 24%) [1]. In comparison with this data, our study showed a slightly higher prevalence of 27% moderate to severe bone marrow oedema–like lesions. Clinically, this may be of importance as bone marrow lesions are linked to the onset of osteoarthritis [28–30].

Prevalence of ligament tears was 0% for 16 of the 20 studies, with the remaining four studies reporting 1–30% of mostly anterior cruciate or collateral ligament partial tears [1]. Similarly, our results showed no complete tears and a low prevalence of 3% partial ligamentous tears, of the anterior cruciate and lateral collateral ligaments.

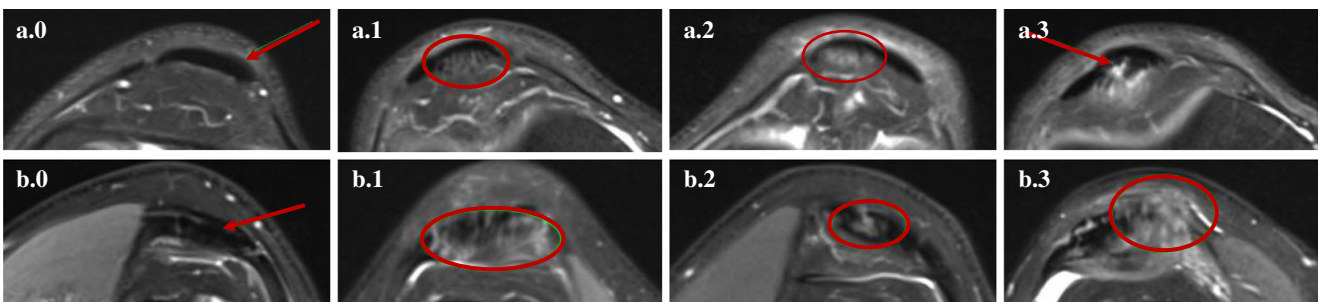

Fig. 3 Axial proton-density fat-saturated MR images of (a) patellar tendons (a.0, grade 0; in the left knee of a 40-year-old man; a.1, grade 1; in the right knee of a 62-year-old man; a.2, grade 2; in the left knee of a 56-year-old man; a.3, grade 3; in the right knee of a 44-year-old man) and (b) quadriceps tendons (b.0, grade 0; left knee of a 40-year-old man; b.1, grade 1; in the right knee of a 40-year-old woman; b.2, grade 2; in the left knee of a 44-year-old man; b.3, grade 3; in the right knee of a 48-year-old man). The tendons are indicated by red arrows or circles; grade 0: normal tendon appearances; grade 1: increased signal intensity in less than 25% of the axial cross-sectional tendon width; grade 2: increased high-signal intensity in 25 to 50% of the axial cross-sectional tendon width; grade 3: increased high-signal intensity occupying more than 50% of the axial cross-sectional tendon width

Table 5 Number of participants with both knees or single knees showing abnormalities on MRI, respectively, and total number of knees affected, in those aged < 40 and ≥ 40, respectively, in the meniscus, articular cartilage, bone marrow, tendons and ligaments

Key knee abnormalities	Participants (%) with both knees affected	Participants (%) with single knees affected		Total knees (%) affected		
		Right knee	Left knee	Right knee	Left knee	All knees
Aged < 40 (N = 25, 50 knees)						
Meniscal tears	2 (8%)	4 (16%)	0 (0%)	6 (12%)	2 (4%)	8 (16%)
Cartilage abnormalities	7 (28%)	3 (12%)	2 (8%)	10 (20%)	9 (18%)	19 (38%)
Bone marrow oedema	8 (32%)	3 (12%)	2 (8%)	11 (22%)	10 (20%)	21 (42%)
Tendon abnormalities	5 (20%)	6 (24%)	2 (8%)	11 (22%)	7 (14%)	18 (36%)
Ligament abnormalities	3 (12%)	7 (28%)	1 (4%)	10 (20%)	4 (8%)	14 (28%)
Aged ≥ 40 (N = 90, 180 knees)						
Meniscal tears	21 (23%)	4 (4%)	16 (18%)	25 (14%)	37 (20%)	62 (34%)
Cartilage abnormalities	54 (60%)	10 (11%)	6 (7%)	64 (36%)	60 (33%)	124 (69%)
Bone marrow oedema	39 (43%)	12 (13%)	8 (9%)	51 (28%)	47 (26%)	98 (54%)
Tendon abnormalities	26 (29%)	20 (22%)	16 (18%)	46 (26%)	42 (23%)	88 (49%)
Ligament abnormalities	25 (28%)	9 (10%)	14 (16%)	34 (19%)	39 (22%)	73 (41%)

Regarding asymptomatic knee tendon abnormalities, there is not much evidence in the literature about their incidence. Matiotti SB et al. [31] identified 19.5% tendon injuries in asymptomatic soccer players—adolescents—and we identified a prevalence of 26% cases of tendon abnormalities in our study. The observation of asymptomatic patellar tendonitis may suggest that this type of injury could result in future symptoms future and encourages closer monitoring of these cases [31–34].

The prevalence of lesions was reported to increase with age [1]; this is in agreement with our study outcomes. Also we showed that overweight people are more predisposed to load-bearing tendon thickness, finding which is supported by previous studies [35–39].

Study strengths and limitations

The main study strengths are the large sample size, the methodology employed in the study (3.0 T MRI and multichannel coil) and the detailed analysis of knee structures. As compared with the clinically widely used 1.5 T system, 3.0 T MRI reported higher diagnostic confidence for better visualisation of the morphology and pathology of joint structures [5, 6, 40]. Also, the multichannel technology offers additional benefits of higher spatial resolution and increased diagnostic quality [13, 14]. So far 11 studies have employed the 3.0 T MRI technique for the assessment of knee structures and the sample size did not exceed 95 asymptomatic knees in any MRI trial [41–51]. This study involves the highest number of knees that were ever scanned with 3.0 T MRI, in particular of asymptomatic sedentary older adults. Additionally, we did an in-depth analysis of all structures and reported the prevalence of lesions by levels of severity instead of reporting only the abnormalities irrespective of grade.

We acknowledge the following limitations: (1) MRI double-reporting was done for 20% of the cohort; however, no major discrepancies between the radiologists' reports were identified in this subset of images so the single-reporting of the remaining scans was considered to be reliable; (2) the KOOS questionnaires, the history of any past joint problems and the activity levels of volunteers were self-reported; therefore, a risk of bias needs to be considered; (3) the analysis was confined to one ethnic group, thus limiting the potential generalisation of the findings; (4) meniscal assessment included both meniscal horns, except for the body; therefore, few lesions could have been missed; (5) follow-up studies are needed to investigate the clinical relevance of the findings over time.

Conclusions and clinical significance

Our study questions clinical decision-making regarding arthroscopy and its efficacy in reducing symptoms and treatment. The high rate of asymptomatic adults with knee joint abnormalities on MRI may indicate why arthroscopy and other surgical interventions for these do not result in better outcomes than sham surgery [1, 52]. For example, there is no evidence to suggest that meniscectomy benefits patients presenting with meniscal tear symptoms more than sham surgery does [53]. Moreover, meniscectomy and other surgical interventions could lead to further complications or deterioration of the articular cartilage and increase the risk of osteoarthritis [54–56].

Despite the increasing use of high-resolution MRI, in practice, diagnosis should be primarily based on patient's medical history and physical examination by an experienced clinician, instead of solely focusing on the MRI results. The images may

assist in correlating clinical signs and symptoms but should not replace clinical evaluation [57, 58].

Our MRI findings can represent early signs of osteoarthritis and the clinical implications need to be investigated further, including follow-up studies over time, to inform efforts to diagnose and treat knee problems across the lifespan. Further studies could monitor whether the knee condition of those participants with lesions will progress at a faster rate over time than that of those without abnormalities. The findings may guide closer surveillance and prevent future injuries.

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Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The study was approved by NHS Research Ethics Committee (REC Reference Number 15/LO/0086). All participants gave informed consent before taking part.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Can marathon running improve knee damage of middle-aged adults? A prospective cohort study

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ABSTRACT

Objectives To evaluate the short-term impact of long-distance running on knee joints using MRI.

Methods 82 healthy adults participating in their first marathon underwent 3T (Tesla) MRI of both knees 6 months before and half a month after the marathon: 71 completed both the 4 month-long standardised training programme and the marathon; and 11 dropped-out during training and did not run the marathon. Two senior musculoskeletal radiologists graded the internal knee structures using validated scoring systems. Participants completed Knee Injury and Osteoarthritis Outcome Score questionnaires at each visit for self-reporting knee function.

Results Premarathon and pretraining MRI showed signs of damage, without symptoms, to several knee structures in the majority of the 82 middle-aged volunteers. However, after the marathon, MRI showed a reduction in the radiological score of damage in: subchondral bone marrow oedema in the condyles of the tibia (p=0.011) and femur (p=0.082). MRI did also show an increase in radiological scores to the following structures: cartilage of the lateral patella (p=0.0005); semimembranosus tendon (p=0.016); iliotibial band (p<0.0001) and the prepatellar bursa (p=0.016).

Conclusion Improvement to damaged subchondral bone of the tibial and femoral condyles was found following the marathon in novice runners, as well as worsening of the patella cartilage although asymptomatic. This is the most robust evidence to link marathon running with knee joint health and provides important information for those seeking to understand the link between long distance running and osteoarthritis of the main weight-bearing areas of the knee.

What are the new findings?

- The main weight-bearing compartments presenting subchondral bone marrow oedema before the marathon, in asymptomatic middle-aged adults, showed reversibility following the training for and completion of running a marathon.
- The patellofemoral compartment was the region most injured by marathon running.
- Marathon running did not result in progression of meniscal tears and their presence did not affect performance.

How might it impact on clinical practice in the future?

- Study findings could help inform marathon running-related decision making.
- During training for a marathon, injury prevention exercises that target those areas of the knee which are more susceptible to damage, especially the patellofemoral joint, should be considered.
- Runners, clinicians and the general public can use this data for a better understanding of the effect of high-intensity exercise on the knee.

INTRODUCTION

Long-distance running has become a popular phenomenon worldwide, with more than 30 million individuals running marathons each year.[1] Running exerts repetitive stress on the lower extremities, especially the knee joint, therefore, in excess, can lead to injuries and the development of osteoarthritis[2 3]

Preparation for a marathon run has been linked to an incidence of musculoskeletal problems as high as 90%,[4] especially at the knee joint including patellofemoral pain.[5] As many participants are first-time runners, with the number of older marathoners being significantly on the rise,[6 7] this has given rise to increasing health concerns.

Few studies have investigated the effects of marathon running on the internal knee structures. MRI is the perfect tool to assess whether running a marathon changes the 'normal structure of the knee', and the high resolution 3 Tesla (T) MRI gives unprecedented precision in detecting subtle changes and pathologies in the structure.[8 9]

Evidence is lacking robustness, as to whether long-distance running, often on hard surfaces such as roads, is bad for the knees. Evidence has relied on small numbers of subjects (<22

participants) and a variety of study designs, for example, low MR field strength (1.5T or less), varying follow-ups, different knee structures being assessed, unclear clinical significance, and differences in the scoring systems used for each knee structure.[1 10–17]

We aimed to better understand the effect of marathon running on the knee joint by performing high resolution 3T MRI scans of both knees of first-time marathon runners before and after running a marathon.

METHODS

Study design and participants

This was a prospective, longitudinal cohort study. All volunteers provided written, informed consent before participation.

We recruited 115 healthy asymptomatic volunteers (51 males, 64 females, median age: 44 years, range: 25–73 years) who were registered for their first marathon (the 2017 London Marathon). The main inclusion criteria were: sedentary,[18] novice marathon runners with no present knee injury/history of knee injury or cardiac abnormalities. Volunteers were screened for good cardiovascular health by our cardiac team who used ECG, exercise stress testing and cardiac MRI. Pregnant women, individuals aged <18 years, experienced runners, with known knee problems or poor cardiovascular health were excluded from the study.

All volunteers underwent bilateral knee 3T MRI scans 2 months before a 4-month standardised gradual training programme for the marathon. Thirty-one of our enrolled cohort failed to complete the training programme and were considered 'non-marathon runners' (see figure 1) due to reasons not directly linked to their pretraining health condition: bradycardia (n=1), bronchitis (n=1), knee pain during training (n=2), calf issue (n=2), plantar fasciitis (n=1), Achilles tendinitis (n=1), metatarsal stress fracture (n=2), personal reasons (n=2) and undisclosed reasons (n=19).

Eighty-three participants completed the marathon, 71 of these attended the clinic for a second MRI scan half a month after the marathon, as did 11 of the 31 non-marathon runners who failed to complete the training and did not start the marathon. Non-marathon runners were used for comparison with the marathon runners' group (figure 1; and table 1 for full participant characteristics).

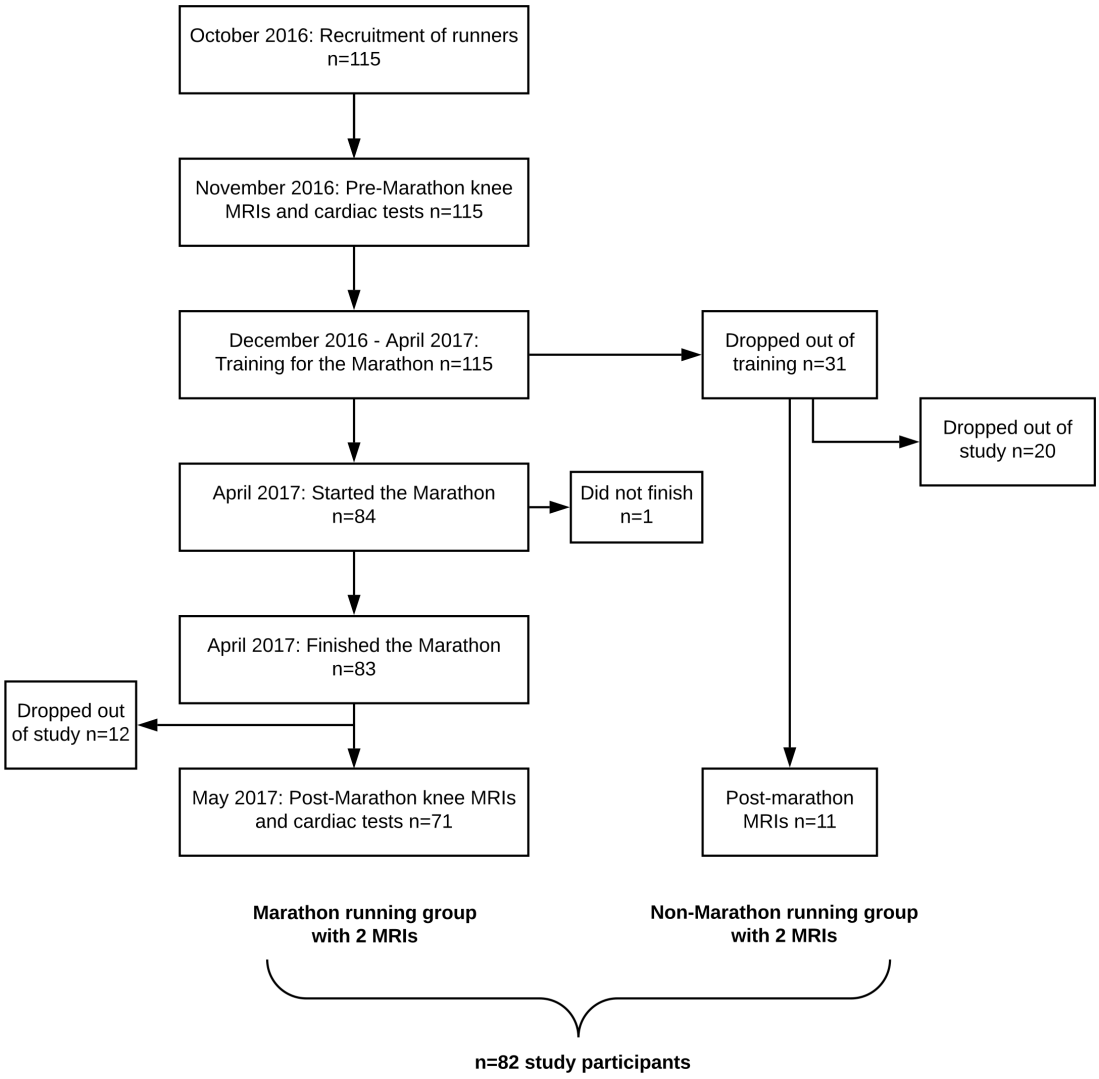

Figure 1 Recruitment and enrolment of study participants.

Table 1 Baseline characteristics of study participants

Characteristics	Marathon runners n=71	Non-marathon runners n=11
Age (years)	44±8.5	44±7.0
BMI (kg/m^2)	25.2±3.6	24.2±2.2*
Height (cm)	171±9.2	176±10.7
Male : Female ratio†	32 : 39	5 : 6

Values are reported as mean±SD for normally distributed data.
*There were two outliers for BMI (≥30kg/m^2) so we excluded those participants from the BMI analysis.
†Average and measure of spread do not apply for categorical data.
BMI, body mass index.

Participant self-assessment questionnaire

The Knee Injury and Osteoarthritis Outcome Score (KOOS) was used as a self-reported questionnaire of the knee condition and associated injuries that can result in osteoarthritis.[19] The assessment is divided into five categories: pain, other symptoms, function in daily living, knee-related quality of life and function in sport and recreation. Participants were asked to complete the questionnaire both before and after the marathon to assess their perceived knee joint health. Each question was provided with five potential answers and marked from zero to four. The sum of the scores from each category was converted into a 0–100 scale, with zero indicating extreme knee problems and 100 indicating no knee problems.

Magnetic resonance imaging

An MRI was performed on each participant 6 months before the marathon (and therefore before the standardised training programme), and then half a month after the marathon. Both knees of marathon runners were analysed using a 3.0 T MR scanner (Prisma, Siemens Healthcare, Erlangen, Germany) and dedicated knee coil. The imaging protocol included proton density-weighted fat suppressed (PD FS) sequences in axial [repetition time (TR) msec/echo time (TE) msec; 4630/37], sagittal (4200/41 ms) and coronal planes (5240/41 ms). All slices were 3 mm thick, with an image size/acquisition matrix of 320×320 pixels. The total acquisition time per bilateral scans was 25 min.

Radiological reporting/image analysis

All MR images were reviewed using a picture archiving and communications system workstation by a musculoskeletal radiologist (AF) with 10 years experience at consultant level. 30% of the cohort (92 MRI scans from two time points of 46 knees from 23 volunteers; randomly-selected) were additionally and independently

Table 2 Number of postmarathon lesions in different structures before and after the marathon/training, in 142 knees of 71 marathon runners and 22 knees of 11 non-marathon runners

Knee abnormalities per structure	Marathon runners (n=142 knees)			Non-marathon runners (n=22 knees)		
	Number of Post-M lesions			Number of Post-M lesions		
	New/ Worsened*	Improved†	Significant change from Pre-M	New/ Worsened	Improved	Significant change from Pre-M
Meniscal tears	1	0	n.s.	0	0	n.s.
Cartilage lesions	25	2	**Lateral patella p=0.0005***	4	0	n.s.
Patello-femoral	21	1		3	0	
Tibio-femoral	4	1		1	0	
BME lesions	26	23	**Medial tibia p=0.011†**	3	3	n.s.
Patello-femoral	19	2		3	1	
Tibio-femoral	7	21		0	2	
Tendon lesions	13	2	**Semimembranosus p=0.016***	2	0	n.s.
Ligament lesions	2	2	n.s.	0	0	n.s.
ITBFS	15	0	**ITB p<0.0001***	1	1	n.s.
Prepatellar bursitis	7	0	**Prepatellar bursitis p=0.016**	1	0	n.s.

All abnormalities were recorded including Grade 1 abnormalities (all grades different from 0 were defined as 'lesions'). P values<0.05 indicate significant changes in the knees between the premarathon and postmarathon time points.See online supplementary appendices 2 and 4 for further details.
*Indicate significant worsening.
†Indicate significant improvement in the extent of lesion.
BME, bone marrow oedema; ITBFS, iliotibial band friction syndrome; n.s., not significant; Post-M, post-marathon; Pre-M, pre-marathon.

Figure 2 MRI scans of a 45 year old marathon runner with finishing time 3 hours and 51 min who was diagnosed during the pretraining period with bucket-handle tear of the posterior horn of the medial meniscus as it is indicated by (A) the sagittal PD FS image (TR=4670, TE=41, slice thickness: 3 mm) (white arrow) and the (B) coronal PD FS image (TR=5240, TE=41, slice thickness: 3 mm) where the meniscal flap within the intercondylar notch (arrow) is shown. The status of the meniscal tear did not change in 2 weeks after the marathon (see C, (D)). PD FS, proton density-weighted fat suppressed; TR, repetition time; TE, echo time.

evaluated, by a second fellowship-trained musculoskeletal radiologist with 9 years experience at consultant level (AHir). The two examiners were blinded to the baseline characteristics of the volunteers. Images of both time points were separately analysed.

In case of discrepancies between the radiologists' evaluation, consensus scores were achieved after consultation.

Quantification of MRI findings

Findings of the knee joint from MRIs were analysed using different validated scoring systems for the presence of any signal changes/lesions of varying severity: menisci,[20 21] cartilage,[22] bone marrow,[23] tendons,[24] ligaments.[21] Other findings were also specified, using a binary scoring system.[25] All abnormalities were recorded including Grade 1 abnormalities (all scores/grades different from zero were defined as 'lesions' throughout the text). The scoring systems are summarised in online supplementary appendix 1.

In addition, we analysed the presence/absence of meniscal tears prior to the run versus the participants' marathon finishing times, to understand whether the presence of asymptomatic meniscal tears affected their performance.

For assessment purposes the patella was divided anatomically into medial and lateral regions, with the ridge being considered as part of the medial region. The tibia was divided into medial and lateral regions and the femur was divided into medial, lateral and trochlea regions and the trochlea was further divided into medial, central, lateral. The medial and lateral menisci were each divided into two subregions: anterior horn and posterior horn. Scores were assigned for each individual region.

Statistical analysis

Both knees of the same subject were examined and each knee was treated independently in the statistical analysis. The data was summarised and then comparisons were made between groups of data. Unpaired t-test was used to assess any significant differences between marathon runners and non-marathon runners with respect to age and height. Two sample t-test was used to assess any significant differences between the two groups with respect to body mass index (BMI). χ^2 test was used for comparison of gender differences between the two groups. Changes between premarathon and postmarathon BMI were analysed using paired t-test in marathon runners and non-marathon runners, respectively. Wilcoxon test was used to assess significant differences between 6 months premarathon and half a month postmarathon scores/grades for each knee feature, as well as premarathon and postmarathon participant KOOS results for each questionnaire item. Statistical significance was defined as $p<0.05$ (GraphPad Prism, V.6.0 c).

Patient and public involvement

This research would not have been possible without the involvement of the runners who were successful in the ballot for the London Marathon 2017 and volunteered to participate in the study. No participants were directly involved in the design, recruitment, or conduct of the study. However, the participants were made aware of their contribution of clinical data to research through their informed consents. After publication, dissemination of the results will be sought across social media and scientific meetings. Also, a summary report of the study results was sent to participants informing them about our findings and implications.

RESULTS

Before the marathon, 115 volunteers underwent MRI of both knees (230 MRI scans) and 82 out of them came back for another set of scans after the marathon and/or training (164 MRI scans). Here, we report any changes seen in the 164 knees when the premarathon MRI was compared with the postmarathon MRI for each knee structure. We have also compared findings between the runners (n=71, 142 knees) and the non-marathon runners (n=11, 22 knees). Full details were given in online supplementary appendix 2.

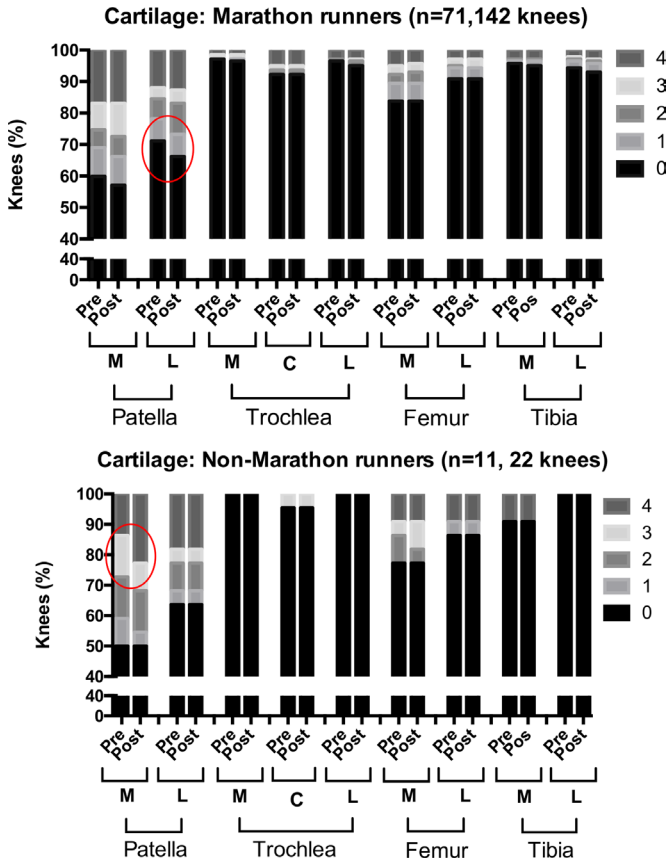

Figure 3 The prevalence of knees with premarathon and postmarathon cartilage lesions in marathon runners and non-marathon runners. The lesions were graded using the modified Noyes and Stabler scoring system and scores 0–4 were assigned: 1—areas of heterogeneous signal intensity on fat saturated IW FSE sequences; 2—cartilage defects that involve less than 1/2 of cartilage thickness; 3—cartilage defects that involve more than 1/2 of cartilage thickness but less than full thickness. 4—full thickness cartilage defects exposing the bone. Red circles indicate changes in the grading of lesions in the knees of participants between the premarathon and postmarathon scans. C, central; L, lateral; M, medial; IW FSE, intermediate-weighted fast spin-echo.

Participant characteristics

There were no significant differences between the two groups of volunteers (marathon and non-marathon runners) with regards to age (p=0.795), BMI at the beginning of the study (p=0.375), height (p=0.264) and gender (0.981).

A significant difference between preBMI and postBMI datasets in marathon runners (p=0.009) were noted and no significant difference in non-marathon runners (p=0.800) (see online supplementary appendix 3). The majority of marathon runners (67%) reduced their BMI as a result of the marathon training, with the median value reduced from 25.2±3.6 to 24.9±3.5.

The mean marathon finishing time was 5 hours 20 min.

KOOS analysis

Seventy out of the 82 participants completed KOOS questionnaires both before and after the marathon: 65/71 marathon runners and 5/11 non-marathon runners. Both premarathon and postmarathon KOOS scores in marathon runners and non-marathon runners were normally distributed. No significant changes between premarathon and postmarathon KOOS scores were identified in runners for the individual questionnaire items related to: symptoms (p=0.981), pain (p=0.121), daily activity (p=0.303), sports and recreational activities (p=0.133), quality of life (p=0.096). No significant differences between the same two scanning time points were reported among non-marathon runners: symptoms (p=0.375), pain (p=0.250), daily activity (p>0.999), sports and recreational activities (p p>0.999), quality of life (p=0.250) (see online supplementary appendix 3).

Meniscus

Before the marathon, 51 (36%) of 142 knees, of those who finished the marathon, had meniscal tears (figure 2) and 23 knees (16%) had meniscal signal hyperintensity. There were no significant differences in prevalence of meniscal lesions between premarathon and postmarathon scans. After the marathon, only one runner showed an increased grade from a normal meniscus to horizontal tear in the left knee (table 2; 40-year-old woman; marathon finishing time: 6 hours 20 min). Menisci of all other scanned knees remained unchanged. The majority of the meniscal lesions (83%) were seen in the posterior horn of the medial meniscus.

Out of the 84 participants who entered the race, 37 were diagnosed with meniscal tears and 47 were tear-free at the premarathon/pretraining MRI scan (online supplementary appendix 5). Only one participant who had a meniscal tear did not finish the marathon and this participant was not included in the statistical analysis. There was no significant difference in the finishing times between the two groups (meniscal tear present/meniscal tear absent) (p=0.135; online supplementary appendix 5).

In non-marathon runners, six out of 22 knees (27%) had meniscal tears and five knees (23%) presented with meniscal signal hyperintensity at the first time point of scanning. No change was seen after the marathon (table 2).

Articular cartilage

Before the marathon, more than half of the knees, of those that went on to finish the marathon, already had cartilage damage (92 knees, 65%), with the majority of lesions located in the patellofemoral joint (70%) and all were asymptomatic. The patellofemoral joint was most affected after the marathon (21 cartilage lesions), especially the lateral patellar facet (12 lesions, p=0.0005; table 2; figure 3; online supplementary appendix 6 – figure 2; online supplementary appendices 7 and 8).

Similarly, in non-marathon runners, more than half of the knees had cartilage lesions (15 out of 22 knees, 68%) prior to training. After training, four lesions worsened (table 2), with three of them being located in the patella (online supplementary appendix 8).

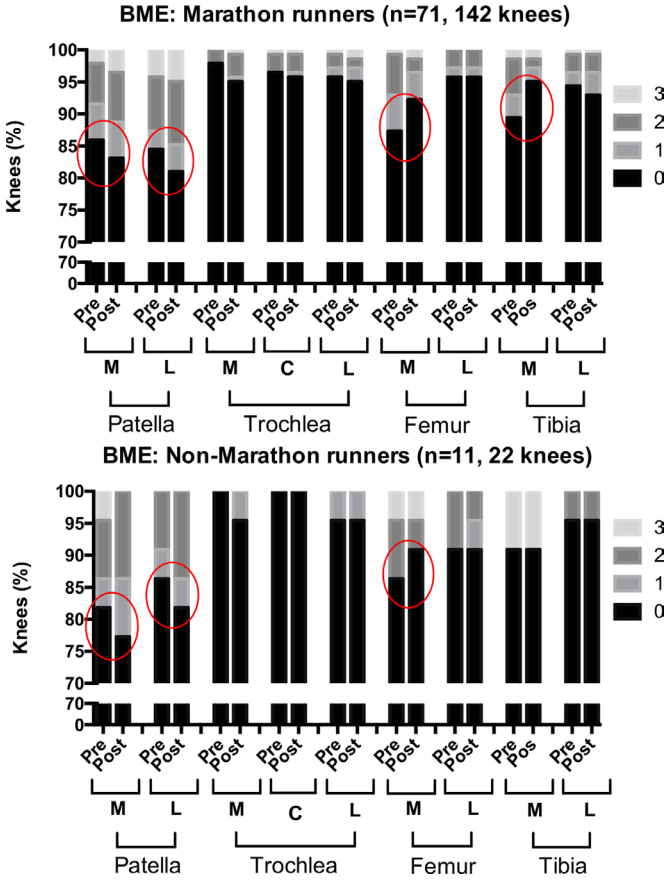

Figure 4 The prevalence of knees with premarathon and postmarathon subchondral BME in marathon runners and non- marathon runners. The lesions were graded using the KOSS scoring system and scores 0–3 were assigned: 0—absent; 1—minimal (d<5 mm); 2—moderate (d=5–20 mm); 3—severe (d>=20 mm). Red circles indicate changes in the grading of lesions in the knees of participants between the premarathon and postmarathon scans. BME, bone marrow oedema; C, central; d, diameter; KOSS, Knee Osteoarthritis Scoring System; L, lateral; M, medial.

Subchondral bone marrow

Before the marathon, subchondral bone marrow oedema (BME) was present in 58 knees (41%), of those that went on to finish the marathon, with over half of the lesions in the patella-femoral joint (54%) (figure 4) After the marathon, the patellofemoral joint had the highest number of new/worsened lesions (19 lesions; table 2; online supplementary appendix 6 – figures 3 and 4), although of no statistical significance. However, improvement was noted in the medial compartment BME with 10 lesions improved in the tibia (p=0.011) and nine lesions improved in the femur (p=0.082; table 2;online supplementary appendices 7 and 8). In non-marathon runners, nine out of 22 knees (41%) had BME before training. After training, there were three additional patellar lesions and three other lesions improved (online supplementary appendix 6 – figure 4; online supplementary appendix 7).

Tendons

Before the marathon, tendon injuries were present in 60 knees (42%), of those that went on to finish the marathon, with the majority being patellar tendon, followed by quadriceps, semimembranosus tendon and lastly a small number of other tendons. Postmarathon, six new insertional semimembranosus tendon injuries appeared (p=0.016; table 2; online supplementary appendices 5 and 6). In non-marathon runners, five knees (23%) had tendon lesions before training. Post-training, two previously healthy knees developed patellar tendon lesions (table 2; online supplementary appendix 7).

Ligaments

Before the marathon, 59 knees (42%), of those that went on to finish the marathon, had ligamentous lesions, with the vast majority being found in the anterior cruciate ligament (ACL; 90%), and few in the medial collateral ligament (MCL; 7%) and lateral collateral ligament (LCL; 3%; table 2).

Only the collateral ligaments were minimally changed after the run: medial (two lesions resolved), lateral (two lesions appeared; table 2; online supplementary appendices 7 and 8). In non-marathon runners, seven knees (32%) had ligamentous lesions before training. No change was recorded after the training (table 2; online supplementary appendix 7).

Other findings

Before the marathon, a number of marathon runners' knees had: joint effusion (52%), Baker's cyst (34%), prepatellar bursitis (25%) and iliotibial band friction syndrome (ITBFS) (2%).

After the marathon, there was a significant increase in the number of knees with prepatellar bursitis (seven lesions; p=0.016) and ITBFS (15 lesions; p<0.0001) (table 2). Similarly, joint effusions (50%), Baker's cysts (41%) and prepatellar bursitis (27%) were prevalent in non-marathon runners before the training. After training, the levels of these remained almost unchanged.

Dual reporting

No major discrepancies between the scores of the two radiologists were reported (30% participants). For patellar cartilage we found differences in the radiologists' scores in 30% of the scans at the two time points, but consensus scores were achieved after consultation between radiologists.

DISCUSSION

Principal findings

Data from MRI scans of 164 knees from 82 novice, middle-aged marathon runners found damage in some areas of the knee (lateral patella cartilage and bone, the iliotibial band) and improvement in other areas (subchondral bone of the femoral and tibial condyles) as a result of training for, and running a marathon. Meniscal damage did not prevent marathon running.

Strengths and weaknesses

Crucial to this study design was the recruitment of middle-aged volunteers because they had a large number of asymptomatic knee abnormalities on MRI prior to training/running: this enabled us to examine both increased and decreased damage to identify those structure at risk and those that benefit from long distance running. Additionally, this is the largest and most detailed study of the knees of middle-aged marathon runners. Detailed assessment of each knee structure was made from 3T MRI, which is the highest resolution in clinical use and enabled greater diagnostic confidence.[8 9]

We acknowledged the following limitations: first, MRI reporting involves a certain level of bias but we tried to minimise it by involving two independent radiologists in the image analysis. Second, prestudy lifestyle details such as sport activities were not available and could not be accounted for; however, the participants were sedentary at recruitment and followed a standardised training programme premarathon. Lastly, the exact times of dropping out from training by non-marathon runners were unavailable and could not be commented on.

Comparison with previous studies

Only a few marathon studies have used 3T MRI,[12 15 16] and none of these had a sample size greater than 22.[1 10 12–17] Limitations of these studies include short follow-up and absence of controls.

There is some agreement between our findings and other marathon studies. Similar to our study results, Schueller-Weidekamm *et al*[13] showed no increase in intrameniscal signal intensity after the marathon except in one case. In agreement with our study, signal alterations in the ACL, patellar tendon and joint effusions were seen before the marathon at a relatively high level, with little to no change after the run.[6]

The evidence on BME is conflicting. Stahl *et al*[15] reported BME in 50% of marathon runners' knees and there was an increase in the extent of oedema in 20% of the affected knees after the run. While the majority of other studies[10 12 13] did not show significant bone marrow changes. Our study is the first to show improvement in the subchondral BME as a result of running a marathon.

Schueller-Weidekamm *et al*'s study[13] showed a much lower prevalence of cartilage lesions before the marathon, with 18% knees affected (the specific location of lesions was not reported), while our study had 65% of knees affected. Additionally, they found no change after the run while we found a significant increase in patella cartilage lesions.

Clinical significance

The improvements seen in the BME of the subchondral bone of the medial compartment may suggest that marathon running and/or training could have a protective effect on the knee joints of sedentary asymptomatic individuals.[26–28] Perhaps regular running prevents medial compartment overload due to muscle strengthening.[29 30] Further investigations are needed involving longer follow-up but the implications of these findings are important because subchondral bone marrow defects are linked with the onset of osteoarthritis,[31–33] and exercise is recommended for the treatment of osteoarthritis.

Our study helps to understand the optimal dose of exercise for human knee joints. Marathon training and running may be above the dose recommended for the patellofemoral joint: or recovery treatments should be targeted at this area of the knee. However, marathon seems to be a satisfactory dose of exercise for the medial and lateral tibio-femoral joints.

Before the marathon we found a number of asymptomatic meniscal tears—including bucket-handle tears. After the marathon, the tears did not develop further, supporting conservative/non-surgical management of meniscal injuries in general, if asymptomatic.

Unanswered questions and future research

We question whether the lesions that appeared/worsened from pre-existing ones after the marathon resolve at a long-term follow-up. Further research is required to clarify whether the marathon damage to the knee joint structures is permanent and how serious it is.

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Contributors
LMH, JH, AF, AHir, CT, ADS, SS, JM and AH developed the study concept and design. LMH, JH, AF, CT, ADL, ADS, SS, JM and AH contributed to the acquisition of data. LMH, AF, AHir contributed to the analysis of data. LMH, JH, AF, AHir, JM and AH contributed to the interpretation of data. LMH conducted the statistical analysis. All authors were involved in writing the manuscript. LMH, JH, JM and AH obtained the funding for the study data and analysis. LMH, CT, JM provided administrative, technical, material support for the study analysis. AH is the study supervisor. All authors had full access to the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. AH is the guarantor. The corresponding author LMH attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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SCIENTIFIC ARTICLE

Is the immediate effect of marathon running on novice runners' knee joints sustained within 6 months after the run? A follow-up 3.0 T MRI study

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Abstract

Objective To evaluate changes in the knee joints of asymptomatic first-time marathon runners, using 3.0 T MRI, 6 months after finishing marathon training and run.

Materials and methods Six months after their participation in a baseline study regarding their knee joints, 44 asymptomatic novice marathoners (17 males, 27 females, mean age 46 years old) agreed to participate in a repeat MRI investigation: 37 completed both a standardized 4-month-long training programme and the marathon (marathon runners); and 7 dropped out during training (pre-race dropouts). The participants already underwent bilateral 3.0 T MRIs: 6 months before and 2 weeks after their first marathon, the London Marathon 2017. This study was a follow-up assessment of their knee joints. Each knee structure was assessed using validated scoring/grading systems at all time points.

Results Two weeks after the marathon, 3 pre-marathon bone marrow lesions and 2 cartilage lesions showed decrease in radiological score on MRI, and the improvement was sustained at the 6-month follow-up. New improvements were observed on MRI at follow-up: 5 pre-existing bone marrow lesions and 3 cartilage lesions that remained unchanged immediately after the marathon reduced in their extent 6 months later.

No further lesions appeared at follow-up, and the 2-week post-marathon lesions showed signs of reversibility: 10 of 18 bone marrow oedema-like signals and 3 of 21 cartilage lesions decreased on MRI.

Conclusion The knees of novice runners achieved sustained improvement, for at least 6 months post-marathon, in the condition of their bone marrow and articular cartilage.

Keywords Marathon running · Knee · MRI · Bone · Cartilage

Introduction

So far, previous studies have only found few subtle short-term abnormalities, i.e. non-acute lesions, of low grade of severity; on magnetic resonance imaging (MRI) scans of the knees of regular long-distance runners (minutes to few weeks after the marathon); this was where no significant pre-existing injuries were reported in the first place [1–6]. Limited peer-reviewed data on the impact of marathon running over a longer period of time (medium-term, 2–3-month follow-up; long-term, one study 10-year follow-up) has shown that any immediate post-marathon alterations in MRI signal return to baseline in runners within 3 months [5–8]. All follow-up studies up to this point were conducted with a very small population of regular long-distance runners (up to 13 participants; one knee scanned only) [5–9], and none studied the incidence and status of

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running-related lesions over time in novice runners participating in their first marathon.

To better understand the implications of long-distance running for the knees of novice runners, we aimed to evaluate changes in the knee joints of first-time marathon runners using 3.0 T MRI 6 months after finishing marathon training and run.

Materials and methods

Study design and participants

The study received ethical approval by the UK National Health Service (NHS) Research Ethics Committee and informed consent was obtained from all participants. The volunteers were recruited from the group of runners who were successful in the ballot for the Virgin Money London Marathon 2017. Virgin sent emails to all successful marathon entrants and then a call centre was organized to recruit eligible volunteers for the study.

Only those who had participated in the previous study (study 1 [10]) were included in the follow-up investigation (study 2). Forty-four out of the previous cohort of 82 participants returned for study 2. The reasons for dropping out were not linked to their knee condition but to issues of availability to attend the specific MRI scanning days, i.e. the participants were located across the country.

This was a prospective, longitudinal cohort study of 44 healthy asymptomatic volunteers (17 males, 27 females, median age: 45 years), specifically novice runners who signed up for their first marathon. The main inclusion criteria were as follows: volunteers with no previous running experience and physically inactive before the training for their first marathon, i.e. not meeting physical activity requirements of 30 min of moderate-intensity physical activity, 5 days/week, or 20 min of more intense physical activities, 3 days/week, based on existing health recommendations [11–13]; with no present/previous knee injuries or cardiac abnormalities and no contraindications for undergoing MRI. Exclusion criteria included the following: pregnant women, regular long-distance runners, experienced marathon runners, aged < 18 years, with body mass index (BMI) > 30 OR < 18, with known knee problems, previous knee surgeries or poor cardiovascular health. The participants completed The Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire [14] to ensure good joint function and no symptoms of knee injury.

All participants took part in a standardized 4-month beginner training plan for the marathon developed by Virgin London Marathon (with gradual increase in mileage, freely accessible online). Out of these 44 participants, 37 completed both the training for/and the marathon run (marathon runners), and 7 dropped-out during training (pre-race dropouts) and did not run the marathon, due to various reasons not linked directly to their pre-training health status: bradycardia (n = 1), bronchitis (n = 1), calf issue (n = 1), and personal (n = 4) (see Table 1 for participant characteristics).

Magnetic resonance imaging

The 44 participants were assessed at all 3 time points: (1) 6 months before the race (and therefore before the training programme; MRI 1), (2) 2 weeks after running the marathon (and post-training; MRI 2), and (3) approximately 6 months later (MRI 3). Both marathon runners and pre-race dropouts were scanned at the same 3 time points. Both knees of all participants were scanned and analyzed independently (88 knee MRI scans). At each time point, measurements were performed with the same 3.0 T MR scanner (Prisma, Siemens Healthcare, Erlangen, Germany) and dedicated 15 channel knee coil for the analysis, and identical parameters of the MRI unit were used in order to achieve optimal comparability. The imaging protocol included proton density–weighted fat suppressed (PD FS) sequences in axial (repetition time msec/echo time in msec; 4630/37), sagittal (4200/41 msec) and coronal planes (5240/41 msec). All slices were 3 mm thick, with an image size/acquisition matrix of 320 × 320 pixels. The total acquisition time per bilateral scan was 25 min and average field of view was 16 cm.

The participants were asked to complete KOOS questionnaires on each MRI scanning day to assess their perceived knee condition including symptoms of functional limitation.

Radiological reporting

The assessment of all the MRI data was made by a musculoskeletal radiologist with 10-year experience at consultant level (264 MRI scans, 88 knees × 3 time points). The images from half of the cohort (randomly selected participants) were also evaluated independently by a second fellowship-trained musculoskeletal radiologist with 9-year experience at consultant level. Images of each time point were analyzed separately.

Validated scoring/grading systems [15–20] were used to evaluate the MRI findings. Any signal changes/lesions of various grades of severity were quantified for the following knee structures: meniscus [15, 16], cartilage [17], bone marrow [18], tendons [19] and ligaments [16]. All structural subdivisions were assessed. The presence of other findings was specified [20, 21]. All abnormalities were recorded including grade 1 abnormalities (all scores/grades different from 0 will be defined as ‘lesions’ throughout the text). The main three knee compartments (larger units) include the following: patellofemoral joint; lateral tibiofemoral joint; medial tibiofemoral joint. Full details are presented in Table 2.

In case of discrepancies between the radiologists’ reports concerning the findings, agreement (consensus scores) was

Table 1 Baseline characteristics of study participants. *BMI*, body mass index; *SD*, standard deviation

Characteristics	Marathon runners $n = 37$	Pre-race dropouts $n = 7$
Age (years)*	46.2 ± 9.3	46.6 ± 4.4
BMI (kg/m^2)*	24.5 ± 3.4	23.2 ± 1.5
Height (cm)*	169 ± 8.9	177 ± 12.9
Male:female ratio	13: 24	4: 3
Pre-marathon/pre-training low-intensity physical activity (hours/week)§	2 (0–4)	2 (0–4)

*Values are reported as mean ± SD for normally distributed data

§ Mean (range) are reported

achieved with a consensus reading in a second MRI reporting session.

Statistical analysis

Both knees of the same participant were examined and each knee was treated independently in the statistical analysis. Unpaired *t* test was used to assess any significant differences between the two groups (marathon runners versus pre-race dropouts) with regard to age, BMI and height. Chi-square test was used for comparison of gender differences between the two groups, and of differences between the prevalence of lesions in these groups between MRI 1 and MRI 2, and between MRI 2 and MRI 3, respectively. Wilcoxon matched-pairs signed rank test and paired *t* test were used to assess significant differences between the KOOS results recorded at different time points. Statistical significance for analysis was defined as $p < 0.05$ (GraphPad Prism, version 6.0c).

Results

Participant characteristics

There were no significant differences between the two groups of volunteers (marathon runners and pre-race dropouts) with regard to age ($p = 0.922$), BMI at the beginning of the study ($p = 0.238$), height (0.060) and gender (0.273).

All marathon runners completed the marathon and the mean finishing time was 5 h 18 min. The physical activity varied among participants in the period of time leading to the 6-month follow-up: marathon runners (mean 3 h/week [0–10]); pre-race dropouts (mean: 2 h/week [0–7]).

No significant differences were found between marathon runners and pre-race dropouts in terms of the prevalence and types of changes between MRI scans, in each of the assessed knee structures ($p > 0.005$). No associations could be made between the participants with sustained lesions at follow-up and other known participant characteristics. There were no significant differences in the participants' symptoms/perceived knee condition (KOOS scores) over time, throughout the MRI scanning sessions ($p > 0.05$).

Cartilage

Improvement of pre-marathon cartilage lesions

Two pre-marathon cartilage lesions improved in severity grade (2 runners) from MRI 1 to MRI 2: one in the patellofemoral compartment and one in the tibiofemoral one. The improvement was sustained in both cases at MRI 3 (Table 3).

Six months post-marathon, new improvements in the patellofemoral compartment were seen in 2 runners: 3 pre-marathon lesions which were unchanged from MRI 1 to MRI 2 showed improved state at MRI 3. Similarly, in the pre-race dropouts' group, 3 pre-marathon lesions (in 2 people) improved at MRI 3 (Table 4).

No further lesions appeared at the 6-month follow-up.

Reversibility of post-marathon cartilage lesions

Twenty-one cartilage lesions were found in 13 marathon runners at MRI 2, out of which 13 were new lesions and 8 progressed in extent from the pre-existing lesions at MRI 1; the majority were located in the patellofemoral compartment (17/21; 81%—half were new). Only 4 lesions were observed in the pre-race dropouts' group (3 participants), mostly in the patellofemoral compartment (3/4; 75%). These lesions were not new but progressed from MRI 1 to MRI 2.

In the marathon group, 3/21 (14%) cartilage lesions reversed over time, returning to baseline grading status at MRI 3 (Fig. 1; Table 5).

Bone marrow

Improvement of pre-marathon oedema-like signal

Three cases of pre-marathon bone marrow oedema-like signal showed improved condition (reduction in extent) in 2 runners

Table 2 Knee scoring/grading systems. *BLOKS*, Boston Leeds Osteoarthritis Score; *ACLOAS*, Anterior Cruciate Ligament OsteoArthritis Score; *KOSS*, Knee Osteoarthritis Scoring System; *MOAKS*, MRI Osteoarthritis Knee Score; *WORMS*, Whole-Organ Magnetic Resonance Imaging Score

Scoring system per knee structure	Scores	
BLOKS (0–7 [15]) and ACLOAS (0–8 [16]): Meniscus (medial, lateral) Anterior horn, posterior horn	BLOKS	ACLOAS
	Meniscal signal (not a tear) 0 = Absent 1 = Present	0 = Normal meniscus with absence of tear, maceration and hypointense signal
	Type of tear: 2 = Vertical tear	1 = Intrameniscal hyperintensity not extending to meniscal surface
	3 = Horizontal and radial tear	2 = Horizontal tear
	4 = Complex tear	3 = Radial and vertical tear
	5 = Root tear 6 = Complete maceration	4 = Bucket-handle tear, displaced tear (including root tears) and complex tears
	7 = Meniscal cyst	5 = Meniscal repair
		6 = Partial meniscectomy and partial maceration
		7 = Progressive partial maceration or re-partial meniscectomy (i.e. loss of morphological substance of the meniscus) compared with the previous visit
		8 = Complete maceration or resection
Modified Noyes 0–4 [17]: Cartilage Femur, tibia, patella (medial/-lateral) Trochlea (medial, central, lateral)	0 = Normal 1 = Grade I lesion: have areas of heterogenous signal intensity on fat saturated IW FSE sequences 2 = Grade II lesion: cartilage defects that involve < 1/2 of cartilage thickness 3 = Grade III lesion: cartilage defects that involve > 1/2 of cartilage thickness but < full thickness 4 = Grade IV lesion: full thickness cartilage defects exposing the bone	
KOSS (0–3 [18]): Bone marrow Femur, Tibia, Patella (medial/-lateral) Trochlea (medial, central, lateral)	Bone marrow-oedema like signal 0 = Absent 1 = Minimal (d < 5 mm) 2 = Moderate (d = 5–20 mm) 3 = Severe (d ≥ 20 mm)	
Johnson DP et al. (0–3 [19]): Tendons	0 = Normal tendon appearances 1 = Increased signal intensity in less than 25% of the axial cross-sectional tendon width 2 = Increased high-signal intensity in 25 to 50% of the axial cross-sectional tendon width 3 = Increased high-signal intensity occupying more than 50% of the axial cross-sectional tendon width	
ACLOAS 0–3 [16]: Ligaments	ACL and PCL	MCL and LCL
	0 = Normal ligament with hypointense signal and regular thickness and continuity	0 = Continuous ligament with normal signal, no surrounding hyperintensity/oedema
	1 = Thickened ligament and/or high intraligamentous signal with normal course and continuity	1 = Continuous ligament with normal signal, surrounding hyperintensity reflecting oedema and/or hematoma
	2 = Thinned or elongated but continuous ligament	
	3 = Absent ligament or complete discontinuity	2 = Partial rupture/discontinuity with some preserved fibres
		3 = Complete disruption
WORMS 0–3 [21]: Joint effusion	0 = Absent 1 = < 33% of maximum potential distention 2 = 33–66% of maximum potential distention 3= > 66% of maximum potential distention	
MOAKS 0–3 [20]: Hoffa's synovitis	0 = Absent 1 = Mild 2 = Moderate 3 = Severe	
MOAKS 0–1 [20]: Other findings	0 = Absent 1 = Present	

at MRI 2. The improvement was sustained at MRI 3, so it did not reverse back to MRI 1 condition (Fig. 2a). One pre-race dropout also showed improvement of pre-marathon oedema at MRI 2 and this was maintained at MRI 3. All these were seen in the tibiofemoral knee compartment (Table 3).

At MRI 3, new improvements were identified in the patellofemoral compartment in 4 runners: 4 pre-marathon lesions which were maintained from MRI 1 to MRI 2 reduced in extent at MRI 3 (Fig. 2b); and another one that improved was in the tibiofemoral compartment (Table 4).

No further lesions appeared at the 6-month follow-up.

Table 3 Prevalence and types of improved pre-marathon lesions at MRI 2, with sustained improvement at MRI 3 (by score/grade of severity), in the cartilage and bone marrow. 'Improvement' was defined as reduction in the extent of lesion (score/grade) between MRI scans. The scoring systems were defined in Table 2. *BME*, bone marrow oedema

Knee features per region	Marathon runners				Pre-race dropouts			
	Lesion score/grade			Number of lesions with sustained improvement	Lesion score/grade			Number of lesions with sustained improvement
	MRI 1	MRI 2	MRI 3		MRI 1	MRI 2	MRI 3	
Cartilage lesion								
Patellofemoral	4	3	3	1	–	–	–	–
Medial tibiofemoral	4	2	2	1	–	–	–	–
Lateral tibiofemoral	–	–	–	–	–	–	–	–
Total				2				0
BME-like signal								
Patellofemoral	–	–	–	–	–	–	–	–
Medial tibiofemoral	1	0	0	1	2	0	0	1
Lateral tibiofemoral	2	0	0	1	–	–	–	–
	1	0	0	1	–	–	–	–
Total				3				1

Table 4 Prevalence and types of newly improved pre-marathon lesions at MRI 3 (by score/grade of severity), in the cartilage and bone marrow. 'Improvement' was defined as reduction in the extent of lesion (score/grade) between MRI scans. The scoring systems were defined in Table 2. *BME*, bone marrow oedema

Knee features per region	Marathon runners				Pre-race dropouts			
	Lesion score/grade			Number of lesions with new improvement at MRI 3	Lesion score/grade			Number of lesions with new improvement at MRI 3
	MRI 1	MRI 2	MRI 3		MRI 1	MRI 2	MRI 3	
Cartilage lesion								
Patellofemoral	4	4	3	2	3	3	1	1
	2	2	1	1	2	2	1	1
	–	–	–	–	1	1	0	1
Medial tibiofemoral	–	–	–	–	–	–	–	–
Lateral tibiofemoral	–	–	–	–	–	–	–	–
Total				3				3
BME-like signal								
Patellofemoral	3	3	2	1	–	–	–	–
	2	2	1	1	–	–	–	–
	2	2	0	1	–	–	–	–
	1	1	0	1	–	–	–	–
Medial tibiofemoral	–	–	–	–	–	–	–	–
Lateral tibiofemoral	2	2	1	1	–	–	–	–
Total				5				0

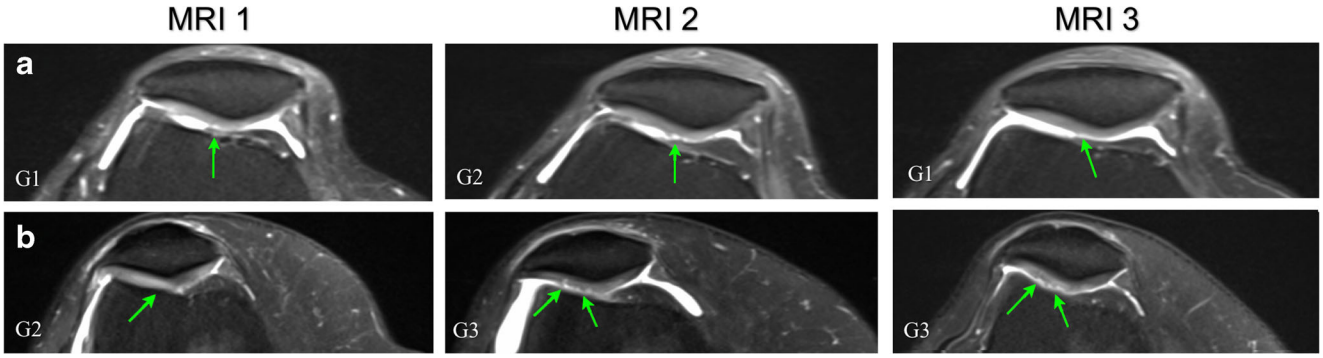

Fig. 1 Axial proton-density fat-saturated MR images of two different knees with changes in the extent of chondral lesions of the patella: A) resolution at 6-month follow-up (MRI 3) of a lesion that previously developed from the pre-marathon scan to the 2 weeks post-marathon scan (MRI 1 to MRI 2), in the right knee of a 67-year-old woman; B) smaller lesion at MRI 3 in comparison to MRI 2. The extent of lesion falls within the same grade parameters; however, it is slightly smaller showing signs of reversibility, in the right knee of a 51-year-old woman. Cartilage abnormalities are indicated by arrows and the lesion grade (G) is included in the left bottom corner and is defined in the modified Noyes scoring system [17] (see Table 2)

Reversibility of post-marathon oedema-like signal

Eighteen bone marrow oedema-like signals were identified in 10 marathon runners at MRI 2: 16 were new and 2 worsened from MRI 1, with the patellofemoral compartment being most affected (15/18; 83%—13 were new lesions). There were 3 new lesions in the pre-race dropouts' group (2 participants), all in the patellofemoral compartment.

Six months later, 10/18 (56%) bone marrow lesions showed reversibility over time, with 8 of them returning to the pre-marathon state (Fig. 3; Table 5). In the pre-race dropouts' group, 1/3 (33%) lesions discovered at MRI 2 showed reversibility.

Table 5 Prevalence and types of reversible lesions (by score/grade of severity) from MRI 1 through to MRI 2 to MRI 3, in the cartilage and bone marrow. 'Reversibility' was defined as resolution/reduction in the extent of those lesions that appeared/progressed at MRI 2 from MRI 1, and then reversed or showed signs of reduction back to MRI 1 grade/score at MRI 3. The scoring systems were defined in Table 2. *BME*, bone marrow oedema

Knee features per region	Marathon runners				Pre-race dropouts			
	Lesion score/grade			Number of lesions that showed reversibility	Lesion score/grade			Number of lesions that showed reversibility
	MRI 1	MRI 2	MRI 3		MRI 1	MRI 2	MRI 3	
Cartilage lesion								
Patellofemoral	0	3	0	1	–	–	–	–
	1	2	1	2	–	–	–	–
Medial tibiofemoral	–	–	–	–	–	–	–	–
Lateral tibiofemoral	–	–	–	–	–	–	–	–
Total				3				–
BME-like signal								
Patellofemoral	0	1	0	2	0	1	0	1
	0	2	0	2	–	–	–	–
	0	3	0	2	–	–	–	–
	0	3	1	1	–	–	–	–
	2	3	1	1	–	–	–	–
Medial tibiofemoral	0	3	2	1	–	–	–	–
Lateral tibiofemoral	0	1	0	1	–	–	–	–
Total				10				1

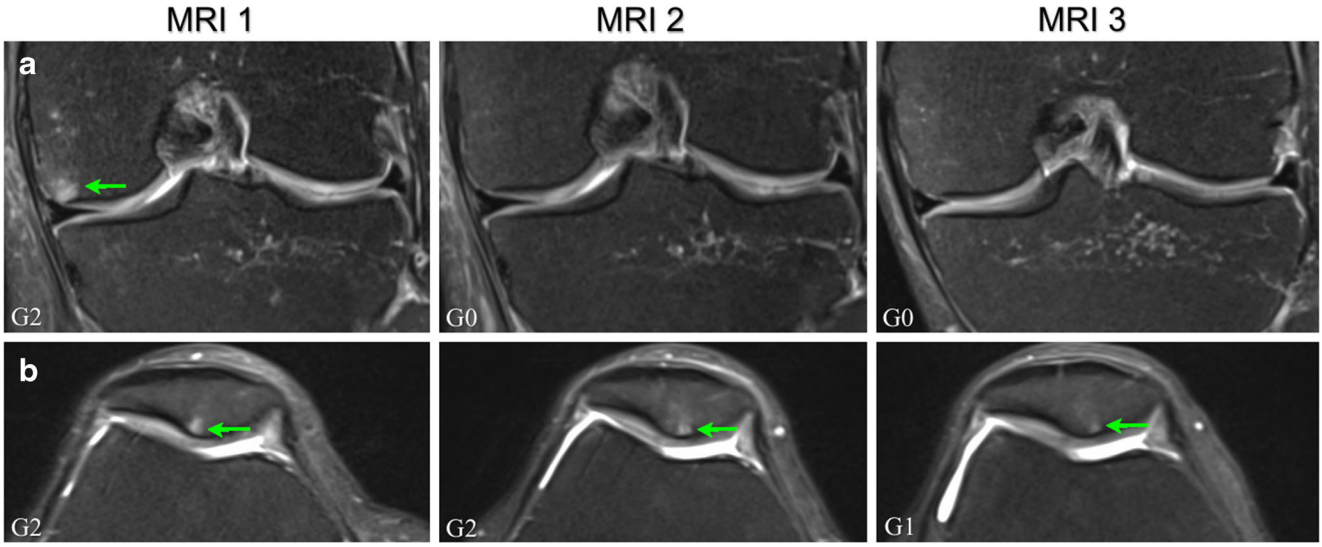

Fig. 2 Coronal and axial proton-density fat-saturated MR images of two different knees with changes in the extent of subchondral bone marrow oedema-like signal: A) sustained improvement at 6-month follow-up (MRI 3) of a previous pre-marathon lesion (MRI 1) that reduced in extent 2 weeks after the marathon (MRI 2), in the femur of the left knee of a 54-year-old man; B) new improvement at MRI 3 in a pre-marathon lesion that remained unchanged from MRI 1 to MRI 2, in the patella of the right knee of a 48-year-old woman. Bone marrow oedema-like signal is indicated by arrows and the lesion grade (G) is included in the left bottom corner and is defined in the KOSS scoring system [18] (see Table 2); KOSS, Knee Osteoarthritis Scoring System

Other findings

Four cases of semimembranosus tendon signal hyperintensity were seen at MRI 2 and one of them showed reversibility at MRI 3. Two ligamentous lesions were discovered in 2 marathon runners at MRI 2 and both reversed at MRI 3. No further development of other lesions was observed.

Discussion

Our study demonstrated that both the training for/and the marathon run may be linked with sustained improvement/regression of pre-marathon bone marrow oedema-like signal and cartilage lesions in novice runners within 6 months after the run. No further lesion acquisition was observed at follow-up, and the few immediate post-marathon lesions showed signs of reversibility. There were no significant differences between marathon runners and pre-race dropouts in terms of results, suggesting that MRI changes may not be attributed to the marathon run alone but to the training as well. This is the first study to show sustained beneficial effect of marathon running on MRI at a 6-month follow-up.

The data adds to the existing literature for the following reasons: (1) the study is the largest to date to assess the effect of marathon running over time using 3.0 T MRI, with the

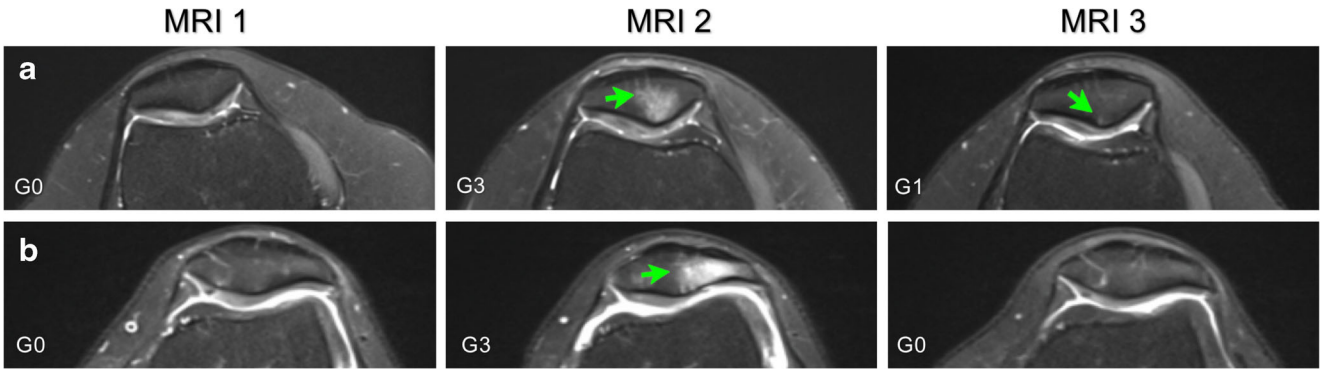

Fig. 3 Axial proton-density fat-saturated MR images of two different knees that showed reversibility at 6-month follow-up (MRI 3) in the extent of subchondral bone marrow oedema-like signal of the patella that previously developed from the pre-marathon scan to the 2 weeks post-marathon scan (MRI 1 to MRI 2): A) reversibility but not to the MRI 1 grading status, in the right knee of a 31-year old woman; B) complete resolution to the MRI 1 grading status, in the left knee of a 34-year-old woman. Bone marrow oedema-like signal is indicated by arrows and the lesion grade (G) is included in the left bottom corner and is defined in the KOSS scoring system [18] (see Table 2); KOSS, Knee Osteoarthritis Scoring System

longest medium-term follow-up. Previous MRI studies involved ≤ 13 runners, follow-ups of up to 3 months and none suggested permanent running-related damage or any sustained beneficial effect on knees [5–8]; (2) our cohort included first-time marathoners, with no running experience before the marathon training, whereas the runners in previous studies had long-distance running experience; (3) the impact of both the training for and the marathon run was assessed, while most previous work studied the knee joints shortly before and after the marathon day, not before training.

We acknowledge the following study limitations: (1) the activity levels of all participants at the beginning of the study and at follow-up were self-reported. The participants could have varied their activity levels and this might have affected the recovery of some lesions more than others; (2) non-runner controls were not involved; however, we included the dropouts from training who did not run the marathon in our analysis; (3) the exact times of dropping out from training by pre-race dropouts were unavailable and could not be commented on; (3) longer term follow-up studies are still needed to clarify the fate of improved lesions in relation to participant characteristics over time, as well as whether complete resolution of remaining lesions occurs later on.

The sustained beneficial effect of running on knees at 6 months after the marathon implies that running may help in reducing the chances of osteoarthritis in the long term. Few other (non-MRI) studies suggested running may protect the knee joint from osteoarthritis [22–25]. Any remaining bone marrow oedema-like signal appearing post-marathon is expected to resolve within 2 years [16, 26–30]. The cartilage may be able to adapt to loads caused by repeated loading during running but recovery time may vary [3, 31].

In conclusion, the knees of first-time marathoners achieved sustained improvement, for at least 6 months post-marathon, in the condition of the bone marrow and articular cartilage.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The study was approved by NHS Research Ethics Committee (REC Reference Number 15/LO/0086). All participants gave informed consent before taking part.

Informed consent Informed consent was obtained from all individual participants included in the study.

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