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Chronic Exercise Does Not Influence The Effects Of Age And Cardiovascular Risk On Carotid Atherosclerosis

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ABSTRACT

PURPOSE: The effect of habitual, high-intensity exercise training on the progression of atherosclerosis is unclear. We assessed indices of vascular health (central systolic blood pressure and arterial stiffness as well as carotid intima medial thickness, or cIMT) in addition to cardiovascular risk factors of trained runners vs. their untrained spouses or partners to evaluate the impact of exercise on the development of carotid atherosclerosis. METHODS: We measured medical and running history, vital signs, anthropometrics, blood lipids, c-reactive protein (CRP), 10 year Framingham risk, central arterial stiffness and systolic blood pressure (SBP) and cIMT in 42 qualifiers (mean age±standard deviation: 46±13 yr, 21 women) for the 2012 Boston Marathon and their sedentary domestic controls (46±12 yrs, n=21 women). RESULTS: Multiple cardiovascular risk factors were reduced in the runners including CRP, non-HDL cholesterol, triglycerides, heart rate, body weight, and BMI (all $p<0.05$). Left and right cIMT, as well as central SBP, were not different between the two groups (all $p>0.31$) and were associated with age (all $r\geq0.41$; $p<0.01$) and Framingham risk score (all $r\geq0.44$; $p<0.01$) independent of exercise group (all $p > 0.08$ for interactions). The amplification of the central pressure waveform (Augmentation pressure at heart rate of 75 beats/min) was also not different between the two groups ($p=0.07$) but was related to age ($p<0.01$) and group ($p=0.02$) in a multiple linear regression model. CONCLUSION: Habitual endurance exercise improves the cardiovascular risk profile, but does not reduce the magnitude of carotid atherosclerosis associated with age and cardiovascular risk factors.

Strengths and Limitations of This Study

- Previous contrasting results on the impact of repetitive strenuous exercise on the development of atherosclerosis might be explained by the impact of multiple lifestyle factors on cardiovascular risk. For example, runners are likely to engage in other health behaviors (in addition to exercise) which could influence atherosclerotic processes and confound interpretation of data.
- Therefore we have used a novel comparison of runners and their non-runner control spouses to conclude that habitual , high-intensity run training improves many aspects of the cardiovascular profile but does not reduce atherosclerosis measured by carotid intima medial thickness (cIMT). Sustained high-intensity aerobic training does not reduce the magnitude of carotid atherosclerotic progression associated with age and disease but also does not appear to exacerbate it.
- We assessed atherosclerosis in our subjects using cIMT, but other procedures such as coronary artery calcium score might provide a better assessment of coronary and cardiovascular disease risk. Our control subjects were also not entirely sedentary. Controls performed less vigorous exercise, but they did perform similar amounts of moderate exercise as the runners. This design may enhance the validity of our study, however, because it might better isolate the influence of habitual, high-intensity exercise training on cardiovascular risk and carotid atherosclerosis.

INTRODUCTION

Carotid intima-medial thickness (cIMT) is a measurement of carotid atherosclerosis and predicts future vascular events such as stroke and heart attack. (1) Moderate habitual physical activity is associated with reduced cardiovascular deaths, but it is not clear if the reduction in cardiac events is due to exercise-induced reductions in atherosclerotic risk factors and atherosclerosis or due to other factors such as enhanced vagal tone, increased electrical stability, and a reduction in sudden death. (2;3)

Several studies have examined atherosclerotic burden in athletes. Galetta and colleagues observed that cIMT was 46% thicker in older adults, but lower in older endurance-trained athletes than sedentary controls, (4) and increased cardiorespiratory fitness is associated with reduced cIMT in healthy (5;6) and diabetic (7) populations. In contrast, Heffernan and colleagues found no significant differences in cIMT scores between exercise trained and age- matched, sedentary (8) men with pre-hypertension. In addition, recent data showed that veteran marathon runners exhibit higher coronary artery calcium scores compared to non-running controls matched for Framingham risk scores (9) and, similarly, male marathon runners display a surprisingly high prevalence of carotid and peripheral atherosclerosis. (10) A recent editorial proposed that repeated bouts of sustained and/or high-intensity aerobic exercise , such as that required for marathon training and competition, evokes systemic vascular remodeling that shifts the effect of aerobic exercise from cardioprotective to atherogenic. (11)

These contrasting results on the impact of repetitive strenuous exercise on the development of atherosclerosis prompted a recent meta-analysis on the effects of exercise on carotid atherosclerosis to conclude that "it remains questionable whether long-term exercise can decelerate the development of carotid atherosclerosis." (12) However, it is possible that discrepant results might also be explained by the impact of multiple lifestyle factors on cardiovascular risk. For example, runners are likely to engage in other health behaviors (in

addition to exercise) which could influence atherosclerotic processes and confound interpretation of data.

Accordingly, the current study compared carotid atherosclerosis measured by cIMT and the cardiovascular risk of runners participating in the 2012 Boston Marathon vs. non-running spouses/domestic partners living in the same household (to control for other lifestyle factors such as diet). In addition to cIMT, we also assessed central systolic blood pressure and arterial stiffness (the amplification of the pressure waveform at the aorta), both of which contribute to central arterial stiffening, smooth muscle hypertrophy and increased intima-medial thickness. (13;14) We hypothesized that the runners would have a more favorable atherosclerotic risk profile and lower cIMT values than the non-runner controls.

METHODS

Forty two runners (50% women) registered for the 116th Boston Athletic Association Marathon (April 16, 2012) and their non-running partners (married/committed and living in the same household) were recruited for the study. All runners had achieved the Boston Athletic Association's qualifying standard and were running the marathon except for 2 runners who were training but not competing that year. Subjects who smoked or with diagnosed cardiovascular or metabolic disease besides hypercholesterolemia were excluded. Controls did not participate in regular, sweat-inducing physical activity ≥ 2 times per week. Subjects provided written, informed consent to participate as approved by the Hartford Hospital Institutional Review Board.

The day before the race subjects provided a medical and running history as well as their training mileage over the 3 months preceding the marathon. Subjects completed the Paffenbarger Physical Activity Questionnaire (15) to calculate average weekly hours of moderate and vigorous activity. Subjects also completed the Block Food Screener (16) to assess dietary intake. Resting blood pressure, heart rate (Welch Allen 52000 Vital Signs Monitor; Skaneateles Falls, NY), height and body weight were measured. Venous blood was obtained after a 12 hour fast to

measure total and high density lipoprotein cholesterol (HDL-C), triglycerides and C-reactive protein (Quest Diagnostics Nichols Institute, Chantilly, VA) . Low density lipoprotein cholesterol (LDL-C) was estimated. (17) Ten year Framingham risk was calculated according to the National Cholesterol Education Program online calculator (http://hp2010.nhlbihin.net/atpiii/calculator.asp).

cIMT was measured with Doppler ultrasound. The artery was imaged 1 cm distal to the right and left carotid bulb using a 5- to 12-MHz multifrequency linear-array transducer attached to a high-resolution ultrasound machine (Terason t3000; Burlington, MA). The image was digitized and edge detection software (Carotid Analyzer; Medical Imaging Applications, Inc., IA) was used to trace the lumen-intima and intima-medial boundaries of the artery over a 1 minute clip to calculate right and left cIMT. Each subject's cIMT data were analyzed by two separate technicians and the two cIMT values were averaged to create a right and left cIMT score. The coefficient of variation between the two technicians measurements was 5.3 ± 2.6 and 6.4 ± 4.0 %, respectively, for right and left cIMT.

Arterial stiffness and central blood pressures were assessed using the SphygmoCor® CPV Central Blood Pressure/Pulse Wave Velocity System (AtCor Medical; Sydney, Australia). Briefly, a tonometer was held on the radial artery to obtain readings of the pulse waveform over 10 seconds. The tonometer transduced dynamic changes in arterial force and volume into a complete pressure waveform calibrated using systolic and diastolic pressure values generated from brachial cuff measurement. A generalized transfer function gain was then applied to the pulse wave derived from the radial artery to reconstruct the aortic pulse and determine the aortic systolic blood pressure as well as the pulse pressure amplification between the aorta and the radial artery. Augmentation index was calculated as the difference in pressure between the systolic shoulder of the ascending pressure curve and the systolic peak, expressed as an absolute value (Augmentation Pressure) and relative to a heart rate of 75 bpm (Augmentation Index @ HR 75).

Statistical analyses were performed with SPSS 15.0 (SPSS, Inc., Chicago, IL). Standard diagnostics were used to determine whether the parametric assumptions (e.g., variance homogeneity, normality) of the models described below were met. Independent samples t-tests were used to examine differences between the running and control groups. Correlations between continuous variables were explored using Pearson coefficients. Additional models using ANOVA (to explore the effect of gender), ANCOVA (to explore the effect of continuous covariates) or multiple linear regression (to investigate the relative influence of relevant factors and their interactions in a multivariate model) were used to determine the influence of various predictors on carotid IMT (or other outcome variables of interest).

RESULTS

Runners and controls were comprised of equal numbers of men and women of similar ages. Runners weighed less and performed more daily vigorous physical activity (Table 1). Runners also demonstrated the expected differences in many cardiovascular risk factors (Table 2). There was a significant correlation between dietary intake patterns in runners and their control spouses (Block Fruit Score: Pearson coefficient = 0.38; $p = 0.02$; Block meat Score: Pearson coefficient = 0.37; $p = 0.02$).

Neither left nor right cIMT differed between runners and controls ($p = 0.31$ and 0.53, respectively). Both left (Figure 1A) and right (Figure 1B) carotid cIMT was associated with age and Framingham risk score (Figure 2A and Figure 2B, respectively) independent of group effects or interactions (all $p > 0.08$).

Aortic SBP was also not different between groups ($p = 0.67$). Aortic SBP was correlated to left cIMT (Pearson coefficient = 0.32; $p < 0.01$) and right cIMT (Pearson coefficient = 0.36; $p < 0.01$), and these associations were not influenced by group effect or interactions (all $p > 0.31$). Similar to cIMT, central SBP was associated with age and Framingham risk ($r = 0.41$ and 0.52; both $p < 0.01$) independent of group effects or interactions (all $p > 0.12$). Carotid augmentation

pressure was not different between groups (p = 0.67) and was related to age (Figure 3A) and calculated Framingham risk score (Figure 3B) independent of group effects or interactions (all p > 0.42). Carotid augmentation pressure was also not different between the two groups (p = 0.07) when expressed relative to a heart rate of 75 beats/min (carotid augmentation index), but this parameter increased with age in both groups and was lower in runners in a multiple linear regression model (Figure 4). There was no relationship between augmentation index and Framingham risk score (all p for effects and interactions > 0.20).

DISCUSSION

This study was, to our knowledge, the first to assess cardiovascular risk biomarkers in trained runners vs. their domestic partners to minimize the influence of lifestyle differences on the effects of chronic, high-intensity exercise. Many aspects of the cardiovascular profile were better in runners vs. controls, and both age and Framingham risk scores were directly related to carotid IMT, but cIMT did not differ between runners and controls. These results suggest that chronic endurance training improves cardiovascular risk parameters, but does not retard the progression of carotid atherosclerosis.

Habitual aerobic exercise improves many cardiovascular risk markers including body weight, (18) blood lipids, (19) and blood pressure, (20) although the individual effect is highly variable. Runners in the current study exhibited 11% lower BMI, 63% lower CRP, 13% lower non-HDL cholesterol, 26% lower triglycerides and 17% higher HDL cholesterol than controls. By contrast, neither left nor right carotid IMT differed between runners and controls. There was a similar lack of effect of marathon training on central systolic blood pressure, which contributes to increases in carotid intima medial thickening with age. (13) These data support recent suggestions that habitual high level physical training may reduce cardiovascular risk factors, but neither reduces nor accelerates atherosclerosis via other mechanisms such as creating vascular turbulence or influencing central blood pressure.

Both age and Framingham risk score were associated with left and right cIMT and central systolic blood pressure, consistent with findings from large-scale epidemiological studies. (21;22) In the current study, these relationships did not differ between trained and untrained adults, suggesting that chronic, high-intensity endurance training does not mitigate the progression of carotid atherosclerosis and intima medial thickening associated with age and cardiovascular risk. Similar findings have been reported in endurance-trained athletes with pre-hypertension, (8) and in older female (23) and male endurance athletes. (13) By contrast, others have documented lower cIMT values in older endurance-trained athletes, (4;24) and shown that 6 months of endurance training lowers cIMT in healthy young men. (25) Discrepancies between these various studies may be attributable to methodological differences such as subjects' age and in the types and duration of habitual endurance training as well as the influence of confounding variables such as diet. Consequently, the current study design in which subjects of a wide age range were studied in comparison to their domestic partners may better isolate the effect of chronic high-intensity chronic endurance training on carotid atherosclerosis and intima-medial thickening.

By contrast, while augmentation pressure did not differ between groups and demonstrated the expected relationship with age and Framingham risk, controlling for heart rate (i.e., assessing augmentation pressure at a uniform heart rate of 75 bpm) demonstrated that this calculated augmentation index was marginally lower ($p = 0.07$) in paired comparisons and statistically lower in a multivariate model when age was taken into account (Figure 4). Augmentation pressure represents the influence of arterial stiffening on the contribution of arterial wave reflections to increasing central blood pressure. Therefore, these data demonstrate once again that chronic aerobic exercise training exerts heterogeneous effects on the vasculature, some of which may be beneficial but not sufficient to alter the progression of atherosclerotic disease.

There have been recent troubling reports suggesting that habitual, prolonged exercise and physical activity and specifically marathon running may actually accelerate atherosclerotic progression. For example, Kroger and colleagues reported an unexpectedly high plaque burden

in the carotid and peripheral arteries of 100 male marathoners. (10) Similarly, coronary artery calcification scores were higher in marathoners than in non-running controls matched for Framingham Risk Score. (9) The current data are reassuring since we did not find more atherosclerosis measured by cIMT in runners relative to their controls,and runners with the highest cIMTs also had the highest Framingham risk scores (Figure 2). These results suggest that habitual exercise may not mitigate atherosclerotic progression, but also does not exacerbate it beyond that attributable to age and risk factors.

Limitations. We assessed atherosclerosis in our subjects using cIMT, but other procedures such as coronary artery calcium score might provide a better assessment of coronary and cardiovascular disease risk. (26;27) These studies were done in a room adjacent to the runners' exposition so that more sophisticated techniques were not available to us. Our control subjects were also not entirely sedentary. Controls performed less vigorous exercise, but they did perform similar amounts of moderate exercise as the runners. This design may enhance the validity of our study, however, because it might better isolate the influence of habitual, high-intensity exercise training on cardiovascular risk and carotid atherosclerosis.

Conclusions. Reports on the impact of long-term aerobic training on atherosclerotic risk are conflicting, and may be confounded by differences in lifestyle factors between subjects. Using a comparison of runners and their non-runner control spouses, we conclude that habitual , high-intensity run training improves many aspects of the cardiovascular profile but does not reduce atherosclerosis measured by cIMT. These data are reassuring given recent reports that marathon running may intensify atherosclerotic disease progression in central and peripheral arteries, and suggest that exercise may reduce cardiovascular events by mechanisms independent of the atherosclerotic process.

FIGURE LEGENDS

Figure 1. Relationships between age and left cIMT (A) and right cIMT (B) with data points represented for each individual subject. Solid line indicates regression line for runners; dashed line indicates regression line for controls.

Figure 2. Relationships between calculated Framingham Risk Score and left cIMT (A) and right cIMT (B) with data points represented for each individual subject. Solid line indicates regression line for runners; dashed line indicates regression line for controls.

Figure 3. Relationships between age and carotid augmentation pressure (A) and calculated Framingham Risk score and carotid augmentation pressure (B) with data points represented for each individual subject. Solid line indicates regression line for runners; dashed line indicates regression line for controls.

Figure 4. Relationship between age and carotid augmentation index with data points represented for each individual subject. Solid line indicates regression line for runners; dashed line indicates regression line for controls.

CONTRIBUTORSHIP

BP, AZ, JC and PT planned the study and wrote the funding proposal. BP, AZ, JC, CT, AB, PD, PT and KB conducted study coordination, data collection and interepretation. BP, AZ, JC, MD and PT wrote the paper. All authors evaluated and revised the paper. BP submitted the paper and is responsible for the overall content as guarantor. The authors also gratefully acknowledge the research assistance provided by Lindsay and Judd Lorson, and William Roman and the logistical support provided by Dave McGillivray and the Boston Athletic Association; and Quest Diagnostics.

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COMPETING INTERESTS

Dr. Paul Thompson is a consultant for Astra Zenica International, Merck & Company, Inc., The Schering-Plough Corporation, Takeda Pharmaceutical Company Limited, Roche, and Genomas and is a member of the speaker's bureau for Merck & Company, Inc., Pfizer, Inc., Abbott Labs, Astra Zenica International, and The Schering-Plough Corporation.

DATA SHARING

There are no additional data available.

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Table 1. Subject Characteristics

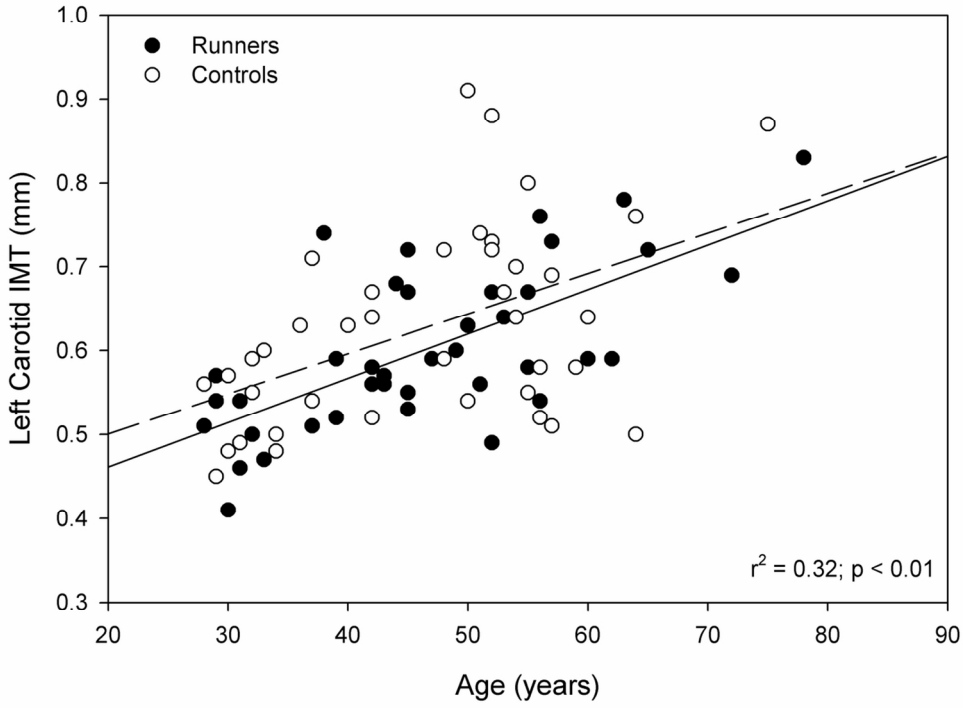
	Runners	Controls
Sample size (n)	42	42
Women (n)	21	21
Age (yrs)	46 ± 13	46 ± 12
Height (inches)	67 ± 5	67 ± 5
Weight (lbs)	149 ± 24*	170 ± 42
Meds (n)		
BP Lowering	1	5
NSAIDS	3	2
Aspirin	1	1
Cholesterol Lowering	2	4
Oral Contraceptives	5	2
Family History of CVD (n)	15	10
Race Time (Hours:minutes)	4:20 ± 0:47	--
Running Mileage	40 ± 16	--
Years Run	12 ± 10	--
Marathons Completed (n)	16 ± 30	--
Average Vig Ex/Day (hr)	2.0 ± 1.1*	0.6 ± 0.6
Average Mod Ex/Day (hr)	3.9 ± 2.2	3.2 ± 2.7
Block Fruit (pts)	18.7 ± 4.2	16.8 ± 4.5
Block Meat (pts)	11.5 ± 5.4	13.1 ± 5.8

BP = Blood pressure; NSAIDS = non-steroidal anti-inflammatories; CVD = cardiovascular disease; Vig Ex = Vigorous Exercise; Mod Ex = Moderate Exercise

Table 2. Cardiovascular Risk Factors

	Runners	Controls
Left cIMT (mm)	0.60 ± 0.09	0.62 ± 0.11
Right cIMT (mm)	0.60 ± 0.11	0.59 ± 0.10
SBP (mmHg)	130 ± 18	127 ± 17
DBP (mmHg)	76 ± 9	75 ± 10
HR (bpm)	57 ± 11*	69 ± 12
BMI (kg/m^2)	24 ± 4*	27 ± 5
Framingham Risk (pts)	3 ± 4	3 ± 3
hsCRP	0.6 ± 0.5*	1.6 ± 1.9
Total-C (mg/dL)	181 ± 29	188 ± 32
Non-HDL-C (mg/dL)	114 ± 31*	131 ± 32
HDL-C (mg/dL)	68 ± 18*	58 ± 16
LDL-C (mg/dL)	99 ± 27	110 ± 28
Triglycerides (mg/dL)	76 ± 29*	103 ± 58
Central SBP (mmHg)	130 ± 18	127 ± 17
Carotid AP (mmHg)	11 ± 8	10 ± 6
AI@HR75 (%)	14 ± 11	20 ± 11

cIMT = carotid intima medial thickness; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; BMI = body mass index; hsCRP = high sensitivity C reactive protein; C = cholesterol; HDL = high density lipoprotein; LDL = low density lipoprotein; SBP = Systolic Blood Pressure; AP = augmentation pressure; AI@HR75 = Augmentation Index at heart rate at 75 bpm.



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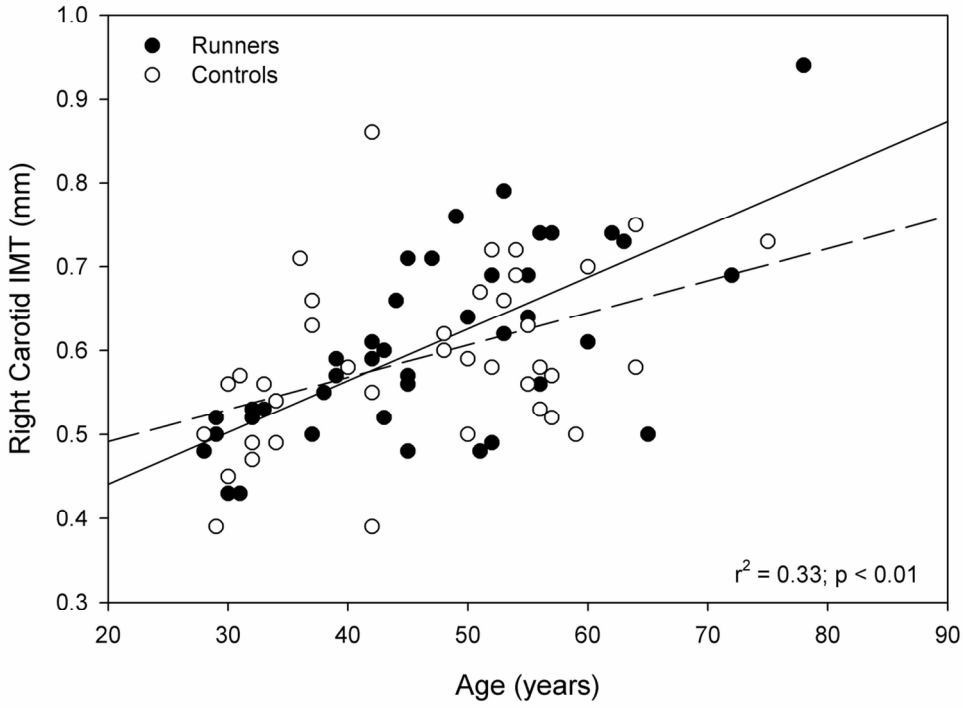

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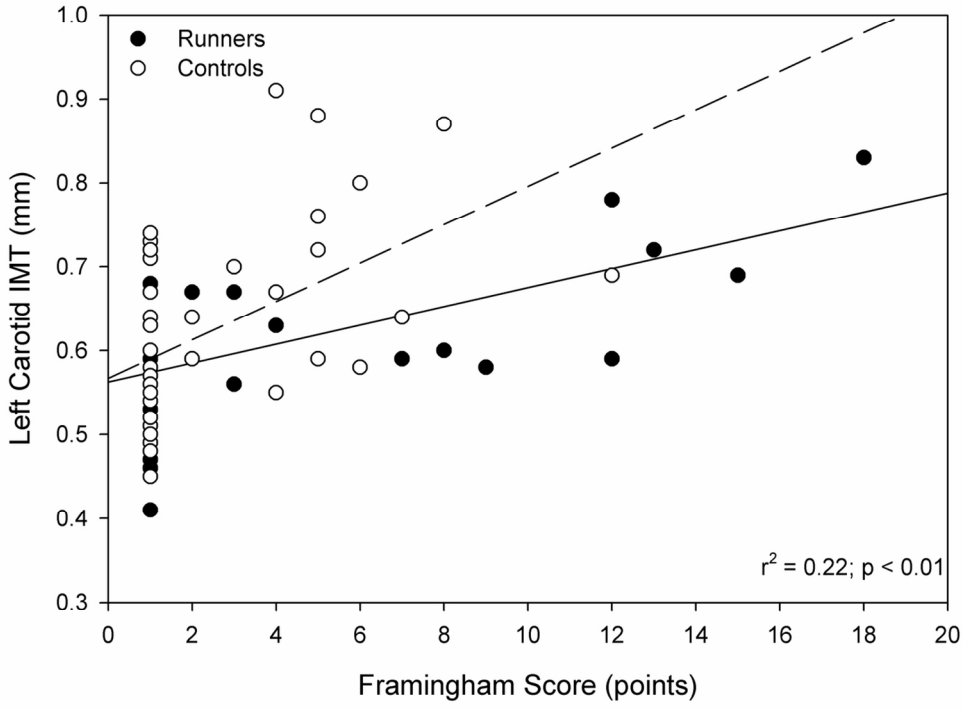

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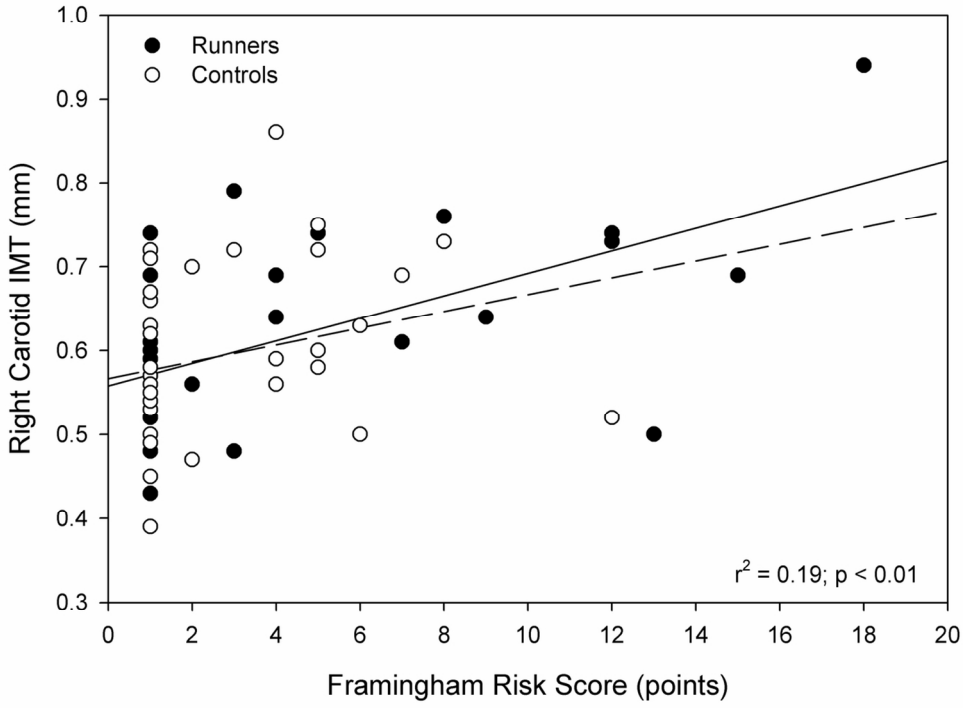

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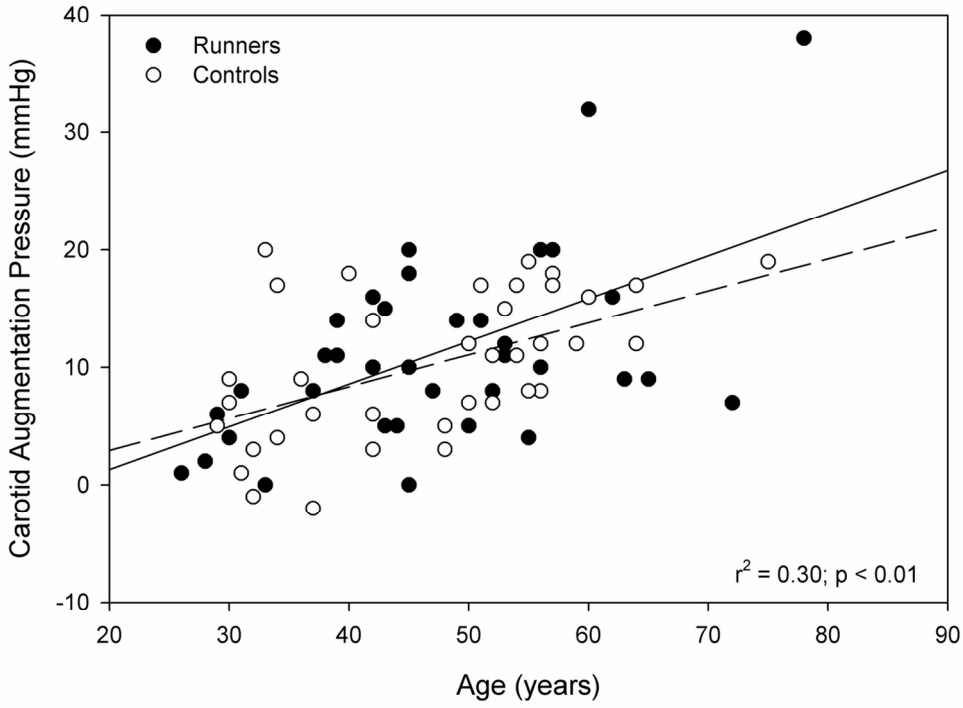

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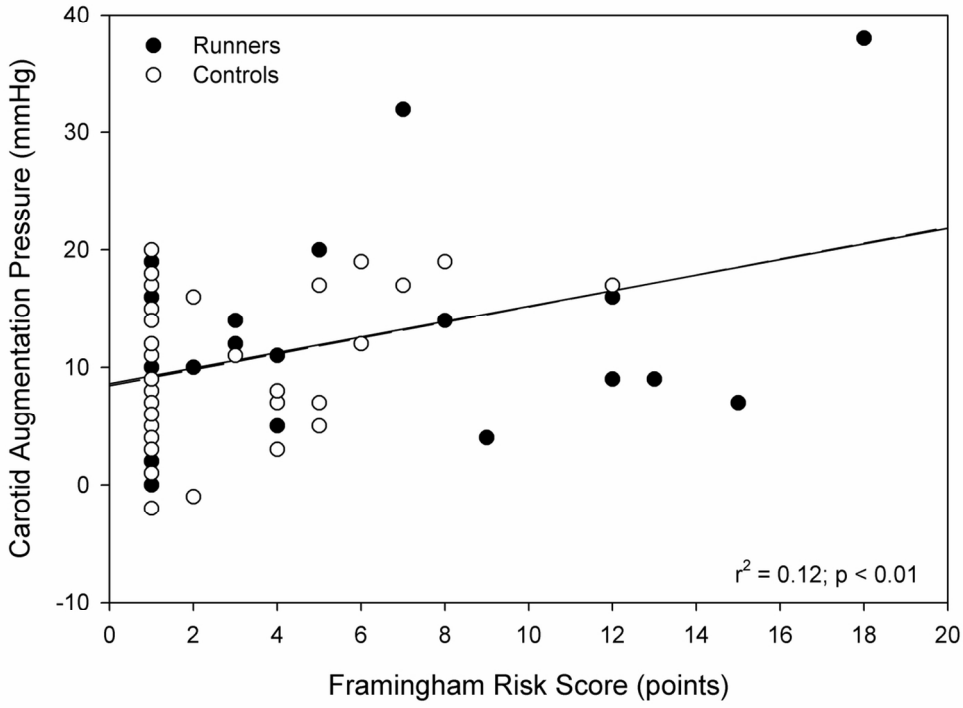

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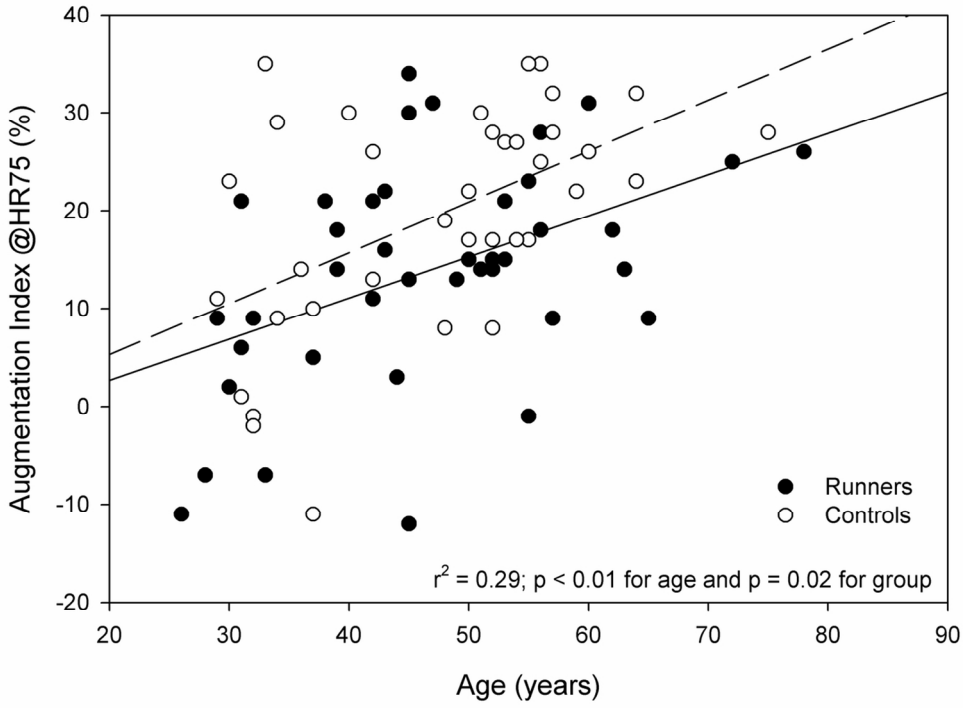

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses Page 5
Methods		
Study design	4	Present key elements of study design early in the paper Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants Page 5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 7
Bias	9	Describe any efforts to address potential sources of bias Page 5
Study size	10	Explain how the study size was arrived at Page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Page 7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
Page 7		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
Page 7		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram

Descriptive data Page 7	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data Page 7	15*	Report numbers of outcome events or summary measures
Main results Page 8	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses Page 8	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results Page 8	18	Summarise key results with reference to study objectives
Limitations Page 10	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation Page 9	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability Page 10	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding Page 11	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Influence of Chronic Exercise on Carotid Atherosclerosis in Marathon Runners

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Influence of Chronic Exercise on Carotid Atherosclerosis in Marathon Runners

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ABSTRACT

PURPOSE: The effect of habitual, high-intensity exercise training on the progression of atherosclerosis is unclear. We assessed indices of vascular health (central systolic blood pressure and arterial stiffness as well as carotid intima medial thickness (cIMT)) in addition to cardiovascular risk factors of trained runners vs. their untrained spouses or partners to evaluate the impact of exercise on the development of carotid atherosclerosis.

METHODS: We measured medical and running history, vital signs, anthropometrics, blood lipids, c-reactive protein (CRP), 10 year Framingham risk, central arterial stiffness and systolic blood pressure (SBP) and cIMT in 42 qualifiers (mean age±standard deviation: 46±13 yrs, 21 women) for the 2012 Boston Marathon and their sedentary domestic controls (46±12 yrs, n=21 women).

RESULTS: Multiple cardiovascular risk factors were reduced in the runners including CRP, non-HDL cholesterol, triglycerides, heart rate, body weight, and BMI (all $p<0.05$). Left and right cIMT, as well as central SBP, were not different between the two groups (all $p>0.31$) and were associated with age (all $r\geq0.41$; $p<0.01$) and Framingham risk score (all $r\geq0.44$; $p<0.01$) independent of exercise group (all $p > 0.08$ for interactions). The amplification of the central pressure waveform (Augmentation pressure at heart rate of 75 beats/min) was also not different between the two groups ($p=0.07$) but was related to age ($p<0.01$) and group ($p=0.02$) in a multiple linear regression model.

CONCLUSION: Habitual endurance exercise improves the cardiovascular risk profile, but does not reduce the magnitude of carotid atherosclerosis associated with age and cardiovascular risk factors.

Strengths and Limitations of This Study

- Previous contrasting results on the impact of repetitive strenuous exercise on the development of atherosclerosis might be explained by the impact of multiple lifestyle factors on cardiovascular risk. For example, runners are likely to engage in other health behaviors (in addition to exercise) which could influence atherosclerotic processes and confound interpretation of data.
- Therefore we have used a novel comparison of runners and their non-runner control spouses to conclude that habitual , high-intensity run training improves many aspects of the cardiovascular profile but does not reduce atherosclerosis measured by carotid intima medial thickness (cIMT). Sustained high-intensity aerobic training does not reduce the magnitude of carotid atherosclerotic progression associated with age and disease but also does not appear to exacerbate it.
- We assessed atherosclerosis in our subjects using cIMT, but other procedures such as coronary artery calcium score might provide a better assessment of coronary and cardiovascular disease risk. Our control subjects were also not entirely sedentary. Controls performed less vigorous exercise, but they did perform similar amounts of moderate exercise as the runners. This design may enhance the validity of our study, however, because it might better isolate the influence of habitual, high-intensity exercise training on cardiovascular risk and carotid atherosclerosis.

INTRODUCTION

Carotid intima-medial thickness (cIMT) is a measurement of carotid atherosclerosis and predicts future vascular events such as stroke and heart attack. (1) Moderate habitual physical activity is associated with reduced cardiovascular deaths, but it is not clear if the reduction in cardiac events is due to exercise-induced reductions in atherosclerotic risk factors and atherosclerosis or due to other factors such as enhanced vagal tone, increased electrical stability, and a reduction in sudden death. (2;3)

Several studies have examined atherosclerotic burden in athletes. Galetta and colleagues observed that cIMT was 46% thicker in older adults, but lower in older endurance-trained athletes than sedentary controls, (4) and increased cardiorespiratory fitness is associated with reduced cIMT in healthy (5) and diabetic (6;7) populations. In contrast, Heffernan and colleagues found no significant differences in cIMT scores between exercise trained and age- matched, sedentary (8) men with pre-hypertension. In addition, recent data showed that veteran marathon runners exhibit higher coronary artery calcium scores compared to non-running controls matched for Framingham risk scores (9) and, similarly, male marathon runners display a surprisingly high prevalence of carotid and peripheral atherosclerosis. (10) A recent editorial proposed that repeated bouts of sustained and/or high-intensity aerobic exercise , such as that required for marathon training and competition, evokes systemic vascular remodeling that shifts the effect of aerobic exercise from cardioprotective to atherogenic. (11)

These contrasting results on the impact of repetitive strenuous exercise on the development of atherosclerosis prompted a recent meta-analysis on the effects of exercise on carotid atherosclerosis to conclude that “it remains questionable whether long-term exercise can decelerate the development of carotid atherosclerosis.” (12) However, it is possible that discrepant results might also be explained by the impact of multiple lifestyle factors on

cardiovascular risk. For example, runners are likely to engage in other health behaviors (in addition to exercise) which could influence atherosclerotic processes and confound interpretation of data.

Accordingly, the current study compared carotid atherosclerosis measured by cIMT and the cardiovascular risk of runners participating in the 2012 Boston Marathon vs. non-running spouses/domestic partners living in the same household (to control for other lifestyle factors such as diet). In addition to cIMT, we also assessed central systolic blood pressure and arterial stiffness (the amplification of the pressure waveform at the aorta), both of which contribute to central arterial stiffening, smooth muscle hypertrophy and increased intima-medial thickness. (13;14) We hypothesized that the runners would have a more favorable atherosclerotic risk profile and lower cIMT values than the non-runner controls.

METHODS

Forty two runners (50% women) registered for the 116th Boston Athletic Association Marathon (April 16, 2012) and their non-running partners (married/committed and living in the same household) were recruited for the study. All runners had achieved the Boston Athletic Association's qualifying standard and were running the marathon except for 2 runners who were training but not competing that year. Subjects who smoked or with diagnosed cardiovascular or metabolic disease besides hypercholesterolemia were excluded. Controls did not participate in regular, sweat-inducing physical activity ≥ 2 times per week. Subjects provided written, informed consent to participate as approved by the Hartford Hospital Institutional Review Board.

The day before the race subjects provided a medical and running history as well as their training mileage over the 3 months preceding the marathon. Subjects completed the Paffenbarger Physical Activity Questionnaire (15) to calculate average weekly hours of moderate and vigorous activity. Subjects also completed the Block Food Screener (16) to assess dietary intake. Resting blood pressure, heart rate (Welch Allen 52000 Vital Signs Monitor; Skaneateles Falls, NY),

height and body weight were measured. Venous blood was obtained after a 12 hour fast to measure total and high density lipoprotein cholesterol (HDL-C), triglycerides and C-reactive protein (Quest Diagnostics Nichols Institute, Chantilly, VA) . Low density lipoprotein cholesterol (LDL-C) was estimated. (17) Ten year Framingham risk was calculated according to the National Cholesterol Education Program online calculator (http://hp2010.nhlbihin.net/atpiii/calculator.asp).

cIMT was measured with Doppler ultrasound. The artery was imaged 1 cm distal to the right and left carotid bulb using a 5- to 12-MHz multifrequency linear-array transducer attached to a high-resolution ultrasound machine (Terason t3000; Burlington, MA). The image was digitized and edge detection software (Carotid Analyzer; Medical Imaging Applications, Inc., IA) was used to trace the lumen-intima and intima-medial boundaries of the artery over a 1 minute clip to calculate right and left cIMT. Each subject's cIMT data were analyzed by two separate technicians and the two cIMT values were averaged to create a right and left cIMT score. The coefficient of variation between the two technicians measurements was 5.3 ± 2.6 and 6.4 ± 4.0 %, respectively, for right and left cIMT.

Arterial stiffness and central blood pressures were assessed using the SphygmoCor® CPV Central Blood Pressure/Pulse Wave Velocity System (AtCor Medical; Sydney, Australia). Briefly, a tonometer was held on the radial artery to obtain readings of the pulse waveform over 10 seconds. The tonometer transduced dynamic changes in arterial force and volume into a complete pressure waveform calibrated using systolic and diastolic pressure values generated from brachial cuff measurement. A generalized transfer function gain was then applied to the pulse wave derived from the radial artery to reconstruct the aortic pulse and determine the aortic systolic blood pressure as well as the pulse pressure amplification between the aorta and the radial artery. Augmentation index was calculated as the difference in pressure between the systolic shoulder of the ascending pressure curve and the systolic peak, expressed as an absolute

value (Augmentation Pressure) and relative to a heart rate of 75 bpm (Augmentation Index @ HR 75).

Statistical analyses were performed with SPSS 15.0 (SPSS, Inc., Chicago, IL). Standard diagnostics were used to determine whether the parametric assumptions (e.g., variance homogeneity, normality) of the models described below were met. Independent samples t-tests were used to examine differences between the running and control groups. Correlations between continuous variables were explored using Pearson coefficients. Additional models using ANOVA (to explore the effect of gender), ANCOVA (to explore the effect of continuous covariates) or multiple linear regression (to investigate the relative influence of relevant factors and their interactions in a multivariate model) were used to determine the influence of various predictors on cIMT (or other outcome variables of interest).

RESULTS

Runners and controls were comprised of equal numbers of men and women of similar ages. Runners weighed less and performed more daily vigorous physical activity (Table 1). Runners also demonstrated the expected differences in many cardiovascular risk factors (Table 2). There was a significant correlation between dietary intake patterns in runners and their control spouses (Block Fruit Score: Pearson coefficient = 0.38; $p = 0.02$; Block meat Score: Pearson coefficient = 0.37; $p = 0.02$).

Neither left nor right cIMT differed between runners and controls ($p = 0.31$ and 0.53, respectively). Both left (Figure 1A) and right (Figure 1B) cIMT was associated with age and Framingham risk score (Figure 2A and Figure 2B, respectively) independent of group effects or interactions (all $p > 0.08$), and age and Framingham risk score were the only significant predictors of cIMT in a multiple linear regression model. To explore whether (in runners only), years spent running influenced the effect of chronic exercise on cIMT, we controlled for years running in a partial correlation analysis of age or Framingham risk score vs. left and right cIMT.

However, in this analysis both left and right cIMT were still associated with age and Framingham risk score, suggesting that years spent running did not influence the relationships between exercise, age, disease risk and cIMT.

Aortic SBP was also not different between groups ($p = 0.67$). Aortic SBP was correlated to left cIMT (Pearson coefficient = 0.32; $p < 0.01$) and right cIMT (Pearson coefficient = 0.36; $p < 0.01$), and these associations were not influenced by group effect or interactions (all $p > 0.31$). Similar to cIMT, central SBP was associated with age and Framingham risk ($r = 0.41$ and 0.52; both $p < 0.01$) independent of group effects or interactions (all $p > 0.12$). Carotid augmentation pressure was not different between groups ($p = 0.67$) and was related to age (Figure 3A) and calculated Framingham risk score (Figure 3B) independent of group effects or interactions (all $p > 0.42$). Carotid augmentation pressure was also not different between the two groups ($p = 0.07$) when expressed relative to a heart rate of 75 beats/min (carotid augmentation index), but this parameter increased with age in both groups and was lower in runners in a multiple linear regression model (Figure 4). There was no relationship between augmentation index and Framingham risk score (all p for effects and interactions > 0.20).

DISCUSSION

This study was, to our knowledge, the first to assess cardiovascular risk biomarkers in trained runners vs. their domestic partners to minimize the influence of lifestyle differences on the effects of chronic, high-intensity exercise. Many aspects of the cardiovascular profile were better in runners vs. controls, and both age and Framingham risk scores were directly related to cIMT, but cIMT did not differ between runners and controls. These results suggest that chronic endurance training improves cardiovascular risk parameters, but does not retard the progression of carotid atherosclerosis.

Habitual aerobic exercise improves many cardiovascular risk markers including body weight, (18) blood lipids, (19) and blood pressure, (20) although the individual effect is highly

variable. Runners in the current study exhibited 11% lower BMI, 63% lower CRP, 13% lower non-HDL cholesterol, 26% lower triglycerides and 17% higher HDL cholesterol than controls. By contrast, neither left nor right cIMT differed between runners and controls. There was a similar lack of effect of marathon training on central systolic blood pressure, which contributes to increases in carotid intima medial thickening with age. (13) These data support recent suggestions that habitual high level physical training may reduce cardiovascular risk factors, but neither reduces nor accelerates atherosclerosis via other mechanisms such as creating vascular turbulence or influencing central blood pressure.

Both age and Framingham risk score were associated with left and right cIMT and central systolic blood pressure, consistent with findings from large-scale epidemiological studies. (21;22) In the current study, these relationships did not differ between trained and untrained adults, suggesting that chronic, high-intensity endurance training does not mitigate the progression of carotid atherosclerosis and intima medial thickening associated with age and cardiovascular risk. This lack of effect was also not explained by differences in years spent running within the runner group, since controlling for duration of running history did not alter the relationships between age, disease risk, and cIMT in runners. Similar findings have been reported in endurance-trained athletes with pre-hypertension, (8) and in older female (23) and male endurance athletes. (13) By contrast, others have documented lower cIMT values in older endurance-trained athletes, (4;24) and shown that vigorous activity reduces the profession of cIMT over 3 years (25) and 6 months of endurance training lowers cIMT in healthy young men. (26) Discrepancies between these various studies may be attributable to methodological differences such as subjects' age and in the types and duration of habitual endurance training as well as the influence of confounding variables such as diet. Consequently, the current study design in which subjects of a wide age range were studied in comparison to their domestic partners may better isolate the effect of chronic high-intensity chronic endurance training on carotid atherosclerosis and intima-medial thickening.

By contrast, while augmentation pressure did not differ between groups and demonstrated the expected relationship with age and Framingham risk, controlling for heart rate (i.e., assessing augmentation pressure at a uniform heart rate of 75 bpm) demonstrated that this calculated augmentation index was marginally lower ($p = 0.07$) in paired comparisons and statistically lower in a multivariate model when age was taken into account (Figure 4). Augmentation pressure represents the influence of arterial stiffening on the contribution of arterial wave reflections to increasing central blood pressure. Therefore, these data demonstrate once again that chronic aerobic exercise training exerts heterogeneous effects on the vasculature, some of which may be beneficial but not sufficient to alter the progression of atherosclerotic disease.

There have been recent troubling reports suggesting that habitual, prolonged exercise and physical activity and specifically marathon running may actually accelerate atherosclerotic progression. For example, Kroger and colleagues reported an unexpectedly high plaque burden in the carotid and peripheral arteries of 100 male marathoners. (10) Similarly, coronary artery calcification scores were higher in marathoners than in non-running controls matched for Framingham Risk Score. (9) The current data are reassuring since we did not find more atherosclerosis measured by cIMT in runners relative to their controls,and runners with the highest cIMTs also had the highest Framingham risk scores (Figure 2). These results suggest that habitual exercise may not mitigate atherosclerotic progression, but also does not exacerbate it beyond that attributable to age and risk factors.

Limitations. We assessed atherosclerosis in our subjects using cIMT, but other procedures such as coronary artery calcium score might provide a better assessment of coronary and cardiovascular disease risk. (27;28) These studies were done in a room adjacent to the runners' exposition so that more sophisticated techniques were not available to us. Our control subjects were also not entirely sedentary. Controls performed less vigorous exercise, but they did perform similar amounts of moderate exercise as the runners. This design may enhance the validity of our

study, however, because it might better isolate the influence of habitual, high-intensity exercise training on cardiovascular risk and carotid atherosclerosis.

Conclusions. Reports on the impact of long-term aerobic training on atherosclerotic risk are conflicting, and may be confounded by differences in lifestyle factors between subjects. Using a comparison of runners and their non-runner control spouses, we conclude that habitual , high-intensity run training improves many aspects of the cardiovascular profile but does not reduce atherosclerosis measured by cIMT. These data are reassuring given recent reports that marathon running may intensify atherosclerotic disease progression in central and peripheral arteries, and suggest that exercise may reduce cardiovascular events by mechanisms independent of the atherosclerotic process.

CONTRIBUTORSHIP

BP, AZ, JC and PT planned the study and wrote the funding proposal. BP, AZ, JC, CT, AB, PD, PT and KB conducted study coordination, data collection and interepretation. BP, AZ, JC, MD and PT wrote the paper. All authors evaluated and revised the paper. BP submitted the paper and is responsible for the overall content as guarantor. The authors also gratefully acknowledge the research assistance provided by Lindsay and Judd Lorson, and William Roman and the logistical support provided by Dave McGillivray and the Boston Athletic Association; and Quest Diagnostics.

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COMPETING INTERESTS

Dr. Paul Thompson is a consultant for Astra Zenica International, Merck & Company, Inc., The Schering-Plough Corporation, Takeda Pharmaceutical Company Limited, Roche, and Genomas and is a member of the speaker's bureau for Merck & Company, Inc., Pfizer, Inc., Abbott Labs, Astra Zenica International, and The Schering-Plough Corporation.

DATA SHARING

There are no additional data available.

FIGURE LEGENDS

Figure 1. Relationships between age and left cIMT (A) and right cIMT (B) with data points represented for each individual subject and r^2 value shown for the entire sample. Solid line indicates regression line for runners; dashed line indicates regression line for controls.

Figure 2. Relationships between calculated Framingham Risk Score and left cIMT (A) and right cIMT (B) with data points represented for each individual subject and r^2 value shown for the entire sample. Solid line indicates regression line for runners; dashed line indicates regression line for controls.

Figure 3. Relationships between age and carotid augmentation pressure (A) and calculated Framingham Risk score and carotid augmentation pressure (B) with data points represented for each individual subject and r^2 value shown for the entire sample. Solid line indicates regression line for runners; dashed line indicates regression line for controls.

Figure 4. Relationship between age and carotid augmentation index with data points represented for each individual subject and r^2 value shown for the entire sample. Solid line indicates regression line for runners; dashed line indicates regression line for controls.

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Table 1. Subject Characteristics

	Runners	Controls
Sample size (n)	42	42
Women (n)	21	21
Age (yrs)	46 ± 13	46 ± 12
Height (inches)	67 ± 5	67 ± 5
Weight (lbs)	149 ± 24*	170 ± 42
Meds (n)		
BP Lowering	1	5
NSAIDS	3	2
Aspirin	1	1
Cholesterol Lowering	2	4
Oral Contraceptives	5	2
Family History of CVD (n)	15	10
Race Time (Hours:minutes)	4:20 ± 0:47	--
Running Mileage	40 ± 16	--
Years Run	12 ± 10	--
Marathons Completed (n)	16 ± 30	--
Average Vig Ex/Day (hr)	2.0 ± 1.1*	0.6 ± 0.6
Average Mod Ex/Day (hr)	3.9 ± 2.2	3.2 ± 2.7
Block Fruit (pts)	18.7 ± 4.2	16.8 ± 4.5
Block Meat (pts)	11.5 ± 5.4	13.1 ± 5.8

BP = Blood pressure; NSAIDS = non-steroidal anti-inflammatories; CVD = cardiovascular disease; Vig Ex = Vigorous Exercise; Mod Ex = Moderate Exercise

Table 2. Cardiovascular Risk Factors

	Runners	Controls
Left cIMT (mm)	0.60 ± 0.09	0.62 ± 0.11
Right cIMT (mm)	0.60 ± 0.11	0.59 ± 0.10
SBP (mmHg)	130 ± 18	127 ± 17
DBP (mmHg)	76 ± 9	75 ± 10
HR (bpm)	57 ± 11*	69 ± 12
BMI (kg/m^2)	24 ± 4*	27 ± 5
Framingham Risk (pts)	3 ± 4	3 ± 3
hsCRP	0.6 ± 0.5*	1.6 ± 1.9
Total-C (mg/dL)	181 ± 29	188 ± 32
Non-HDL-C (mg/dL)	114 ± 31*	131 ± 32
HDL-C (mg/dL)	68 ± 18*	58 ± 16
LDL-C (mg/dL)	99 ± 27	110 ± 28
Triglycerides (mg/dL)	76 ± 29*	103 ± 58
Central SBP (mmHg)	130 ± 18	127 ± 17
Carotid AP (mmHg)	11 ± 8	10 ± 6
AI@HR75 (%)	14 ± 11	20 ± 11

cIMT = carotid intima medial thickness; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; BMI = body mass index; hsCRP = high sensitivity C reactive protein; C = cholesterol; HDL = high density lipoprotein; LDL = low density lipoprotein; SBP = Systolic Blood Pressure; AP = augmentation pressure; AI@HR75 = Augmentation Index at heart rate at 75 bpm.

Influence of Chronic Exercise on Carotid Atherosclerosis in Marathon Runners

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Word Count: 2276

ABSTRACT

PURPOSE: The effect of habitual, high-intensity exercise training on the progression of atherosclerosis is unclear. We assessed indices of vascular health (central systolic blood pressure and arterial stiffness as well as carotid intima medial thickness (cIMT)) in addition to cardiovascular risk factors of trained runners vs. their untrained spouses or partners to evaluate the impact of exercise on the development of carotid atherosclerosis. METHODS: We measured medical and running history, vital signs, anthropometrics, blood lipids, c-reactive protein (CRP), 10 year Framingham risk, central arterial stiffness and systolic blood pressure (SBP) and cIMT in 42 qualifiers (mean age±standard deviation: 46±13 yrs, 21 women) for the 2012 Boston Marathon and their sedentary domestic controls (46±12 yrs, n=21 women). RESULTS: Multiple cardiovascular risk factors were reduced in the runners including CRP, non-HDL cholesterol, triglycerides, heart rate, body weight, and BMI (all $p<0.05$). Left and right cIMT, as well as central SBP, were not different between the two groups (all $p>0.31$) and were associated with age (all $r\geq0.41$; $p<0.01$) and Framingham risk score (all $r\geq0.44$; $p<0.01$) independent of exercise group (all $p > 0.08$ for interactions). The amplification of the central pressure waveform (Augmentation pressure at heart rate of 75 beats/min) was also not different between the two groups ($p=0.07$) but was related to age ($p<0.01$) and group ($p=0.02$) in a multiple linear regression model. CONCLUSION: Habitual endurance exercise improves the cardiovascular risk profile, but does not reduce the magnitude of carotid atherosclerosis associated with age and cardiovascular risk factors.

Strengths and Limitations of This Study

- Previous contrasting results on the impact of repetitive strenuous exercise on the development of atherosclerosis might be explained by the impact of multiple lifestyle factors on cardiovascular risk. For example, runners are likely to engage in other health behaviors (in addition to exercise) which could influence atherosclerotic processes and confound interpretation of data.
- Therefore we have used a novel comparison of runners and their non-runner control spouses to conclude that habitual , high-intensity run training improves many aspects of the cardiovascular profile but does not reduce atherosclerosis measured by carotid intima medial thickness (cIMT). Sustained high-intensity aerobic training does not reduce the magnitude of carotid atherosclerotic progression associated with age and disease but also does not appear to exacerbate it.
- We assessed atherosclerosis in our subjects using cIMT, but other procedures such as coronary artery calcium score might provide a better assessment of coronary and cardiovascular disease risk. Our control subjects were also not entirely sedentary. Controls performed less vigorous exercise, but they did perform similar amounts of moderate exercise as the runners. This design may enhance the validity of our study, however, because it might better isolate the influence of habitual, high-intensity exercise training on cardiovascular risk and carotid atherosclerosis.

INTRODUCTION

Carotid intima-medial thickness (cIMT) is a measurement of carotid atherosclerosis and predicts future vascular events such as stroke and heart attack. (1) Moderate habitual physical activity is associated with reduced cardiovascular deaths, but it is not clear if the reduction in cardiac events is due to exercise-induced reductions in atherosclerotic risk factors and atherosclerosis or due to other factors such as enhanced vagal tone, increased electrical stability, and a reduction in sudden death. (2;3)

Several studies have examined atherosclerotic burden in athletes. Galetta and colleagues observed that cIMT was 46% thicker in older adults, but lower in older endurance-trained athletes than sedentary controls, (4) and increased cardiorespiratory fitness is associated with reduced cIMT in healthy (5) and diabetic (6;7) populations. In contrast, Heffernan and colleagues found no significant differences in cIMT scores between exercise trained and age- matched, sedentary (8) men with pre-hypertension. In addition, recent data showed that veteran marathon runners exhibit higher coronary artery calcium scores compared to non-running controls matched for Framingham risk scores (9) and, similarly, male marathon runners display a surprisingly high prevalence of carotid and peripheral atherosclerosis. (10) A recent editorial proposed that repeated bouts of sustained and/or high-intensity aerobic exercise , such as that required for marathon training and competition, evokes systemic vascular remodeling that shifts the effect of aerobic exercise from cardioprotective to atherogenic. (11)

These contrasting results on the impact of repetitive strenuous exercise on the development of atherosclerosis prompted a recent meta-analysis on the effects of exercise on carotid atherosclerosis to conclude that "it remains questionable whether long-term exercise can decelerate the development of carotid atherosclerosis." (12) However, it is possible that discrepant results might also be explained by the impact of multiple lifestyle factors on cardiovascular risk. For example, runners are likely to engage in other health behaviors (in

addition to exercise) which could influence atherosclerotic processes and confound interpretation of data.

Accordingly, the current study compared carotid atherosclerosis measured by cIMT and the cardiovascular risk of runners participating in the 2012 Boston Marathon vs. non-running spouses/domestic partners living in the same household (to control for other lifestyle factors such as diet). In addition to cIMT, we also assessed central systolic blood pressure and arterial stiffness (the amplification of the pressure waveform at the aorta), both of which contribute to central arterial stiffening, smooth muscle hypertrophy and increased intima-medial thickness. (13;14) We hypothesized that the runners would have a more favorable atherosclerotic risk profile and lower cIMT values than the non-runner controls.

METHODS

Forty two runners (50% women) registered for the 116th Boston Athletic Association Marathon (April 16, 2012) and their non-running partners (married/committed and living in the same household) were recruited for the study. All runners had achieved the Boston Athletic Association's qualifying standard and were running the marathon except for 2 runners who were training but not competing that year. Subjects who smoked or with diagnosed cardiovascular or metabolic disease besides hypercholesterolemia were excluded. Controls did not participate in regular, sweat-inducing physical activity $\geq$ 2 times per week. Subjects provided written, informed consent to participate as approved by the Hartford Hospital Institutional Review Board.

The day before the race subjects provided a medical and running history as well as their training mileage over the 3 months preceding the marathon. Subjects completed the Paffenbarger Physical Activity Questionnaire (15) to calculate average weekly hours of moderate and vigorous activity. Subjects also completed the Block Food Screener (16) to assess dietary intake. Resting blood pressure, heart rate (Welch Allen 52000 Vital Signs Monitor; Skaneateles Falls, NY), height and body weight were measured. Venous blood was obtained after a 12 hour fast to

measure total and high density lipoprotein cholesterol (HDL-C), triglycerides and C-reactive protein (Quest Diagnostics Nichols Institute, Chantilly, VA) . Low density lipoprotein cholesterol (LDL-C) was estimated. (17) Ten year Framingham risk was calculated according to the National Cholesterol Education Program online calculator (http://hp2010.nhlbihin.net/atpiii/calculator.asp).

cIMT was measured with Doppler ultrasound. The artery was imaged 1 cm distal to the right and left carotid bulb using a 5- to 12-MHz multifrequency linear-array transducer attached to a high-resolution ultrasound machine (Terason t3000; Burlington, MA). The image was digitized and edge detection software (Carotid Analyzer; Medical Imaging Applications, Inc., IA) was used to trace the lumen-intima and intima-medial boundaries of the artery over a 1 minute clip to calculate right and left cIMT. Each subject's cIMT data were analyzed by two separate technicians and the two cIMT values were averaged to create a right and left cIMT score. The coefficient of variation between the two technicians measurements was 5.3 ± 2.6 and 6.4 ± 4.0 %, respectively, for right and left cIMT.

Arterial stiffness and central blood pressures were assessed using the SphygmoCor® CPV Central Blood Pressure/Pulse Wave Velocity System (AtCor Medical; Sydney, Australia). Briefly, a tonometer was held on the radial artery to obtain readings of the pulse waveform over 10 seconds. The tonometer transduced dynamic changes in arterial force and volume into a complete pressure waveform calibrated using systolic and diastolic pressure values generated from brachial cuff measurement. A generalized transfer function gain was then applied to the pulse wave derived from the radial artery to reconstruct the aortic pulse and determine the aortic systolic blood pressure as well as the pulse pressure amplification between the aorta and the radial artery. Augmentation index was calculated as the difference in pressure between the systolic shoulder of the ascending pressure curve and the systolic peak, expressed as an absolute value (Augmentation Pressure) and relative to a heart rate of 75 bpm (Augmentation Index @ HR 75).

Statistical analyses were performed with SPSS 15.0 (SPSS, Inc., Chicago, IL). Standard diagnostics were used to determine whether the parametric assumptions (e.g., variance homogeneity, normality) of the models described below were met. Independent samples t-tests were used to examine differences between the running and control groups. Correlations between continuous variables were explored using Pearson coefficients. Additional models using ANOVA (to explore the effect of gender), ANCOVA (to explore the effect of continuous covariates) or multiple linear regression (to investigate the relative influence of relevant factors and their interactions in a multivariate model) were used to determine the influence of various predictors on cIMT (or other outcome variables of interest).

RESULTS

Runners and controls were comprised of equal numbers of men and women of similar ages. Runners weighed less and performed more daily vigorous physical activity (Table 1). Runners also demonstrated the expected differences in many cardiovascular risk factors (Table 2). There was a significant correlation between dietary intake patterns in runners and their control spouses (Block Fruit Score: Pearson coefficient = 0.38; p = 0.02; Block meat Score: Pearson coefficient = 0.37; p = 0.02).

Neither left nor right cIMT differed between runners and controls (p = 0.31 and 0.53, respectively). Both left (Figure 1A) and right (Figure 1B) cIMT was associated with age and Framingham risk score (Figure 2A and Figure 2B, respectively) independent of group effects or interactions (all p > 0.08), and age and Framingham risk score were the only significant predictors of cIMT in a multiple linear regression model. To explore whether (in runners only), years spent running influenced the effect of chronic exercise on cIMT, we controlled for years running in a partial correlation analysis of age or Framingham risk score vs. left and right cIMT. However, in this analysis both left and right cIMT were still associated with age and Framingham

risk score, suggesting that years spent running did not influence the relationships between exercise, age, disease risk and cIMT.

Aortic SBP was also not different between groups ($p = 0.67$). Aortic SBP was correlated to left cIMT (Pearson coefficient = 0.32; $p < 0.01$) and right cIMT (Pearson coefficient = 0.36; $p < 0.01$), and these associations were not influenced by group effect or interactions (all $p > 0.31$). Similar to cIMT, central SBP was associated with age and Framingham risk ($r = 0.41$ and 0.52; both $p < 0.01$) independent of group effects or interactions (all $p > 0.12$). Carotid augmentation pressure was not different between groups ($p = 0.67$) and was related to age (Figure 3A) and calculated Framingham risk score (Figure 3B) independent of group effects or interactions (all $p > 0.42$). Carotid augmentation pressure was also not different between the two groups ($p = 0.07$) when expressed relative to a heart rate of 75 beats/min (carotid augmentation index), but this parameter increased with age in both groups and was lower in runners in a multiple linear regression model (Figure 4). There was no relationship between augmentation index and Framingham risk score (all p for effects and interactions > 0.20).

DISCUSSION

This study was, to our knowledge, the first to assess cardiovascular risk biomarkers in trained runners vs. their domestic partners to minimize the influence of lifestyle differences on the effects of chronic, high-intensity exercise. Many aspects of the cardiovascular profile were better in runners vs. controls, and both age and Framingham risk scores were directly related to cIMT, but cIMT did not differ between runners and controls. These results suggest that chronic endurance training improves cardiovascular risk parameters, but does not retard the progression of carotid atherosclerosis.

Habitual aerobic exercise improves many cardiovascular risk markers including body weight, (18) blood lipids, (19) and blood pressure, (20) although the individual effect is highly variable. Runners in the current study exhibited 11% lower BMI, 63% lower CRP, 13% lower

non-HDL cholesterol, 26% lower triglycerides and 17% higher HDL cholesterol than controls. By contrast, neither left nor right cIMT differed between runners and controls. There was a similar lack of effect of marathon training on central systolic blood pressure, which contributes to increases in carotid intima medial thickening with age. (13) These data support recent suggestions that habitual high level physical training may reduce cardiovascular risk factors, but neither reduces nor accelerates atherosclerosis via other mechanisms such as creating vascular turbulence or influencing central blood pressure.

Both age and Framingham risk score were associated with left and right cIMT and central systolic blood pressure, consistent with findings from large-scale epidemiological studies. (21;22) In the current study, these relationships did not differ between trained and untrained adults, suggesting that chronic, high-intensity endurance training does not mitigate the progression of carotid atherosclerosis and intima medial thickening associated with age and cardiovascular risk. This lack of effect was also not explained by differences in years spent running within the runner group, since controlling for duration of running history did not alter the relationships between age, disease risk, and cIMT in runners. Similar findings have been reported in endurance-trained athletes with pre-hypertension, (8) and in older female (23) and male endurance athletes. (13) By contrast, others have documented lower cIMT values in older endurance-trained athletes, (4;24) and shown that vigorous activity reduces the profession of cIMT over 3 years (25) and 6 months of endurance training lowers cIMT in healthy young men. (26) Discrepancies between these various studies may be attributable to methodological differences such as subjects' age and in the types and duration of habitual endurance training as well as the influence of confounding variables such as diet. Consequently, the current study design in which subjects of a wide age range were studied in comparison to their domestic partners may better isolate the effect of chronic high-intensity chronic endurance training on carotid atherosclerosis and intima-medial thickening.

By contrast, while augmentation pressure did not differ between groups and demonstrated the expected relationship with age and Framingham risk, controlling for heart rate (i.e., assessing augmentation pressure at a uniform heart rate of 75 bpm) demonstrated that this calculated augmentation index was marginally lower ($p = 0.07$) in paired comparisons and statistically lower in a multivariate model when age was taken into account (Figure 4). Augmentation pressure represents the influence of arterial stiffening on the contribution of arterial wave reflections to increasing central blood pressure. Therefore, these data demonstrate once again that chronic aerobic exercise training exerts heterogeneous effects on the vasculature, some of which may be beneficial but not sufficient to alter the progression of atherosclerotic disease.

There have been recent troubling reports suggesting that habitual, prolonged exercise and physical activity and specifically marathon running may actually accelerate atherosclerotic progression. For example, Kroger and colleagues reported an unexpectedly high plaque burden in the carotid and peripheral arteries of 100 male marathoners. (10) Similarly, coronary artery calcification scores were higher in marathoners than in non-running controls matched for Framingham Risk Score. (9) The current data are reassuring since we did not find more atherosclerosis measured by cIMT in runners relative to their controls,and runners with the highest cIMTs also had the highest Framingham risk scores (Figure 2). These results suggest that habitual exercise may not mitigate atherosclerotic progression, but also does not exacerbate it beyond that attributable to age and risk factors.

Limitations. We assessed atherosclerosis in our subjects using cIMT, but other procedures such as coronary artery calcium score might provide a better assessment of coronary and cardiovascular disease risk. (27;28) These studies were done in a room adjacent to the runners' exposition so that more sophisticated techniques were not available to us. Our control subjects were also not entirely sedentary. Controls performed less vigorous exercise, but they did perform similar amounts of moderate exercise as the runners. This design may enhance the validity of our

study, however, because it might better isolate the influence of habitual, high-intensity exercise training on cardiovascular risk and carotid atherosclerosis.

Conclusions. Reports on the impact of long-term aerobic training on atherosclerotic risk are conflicting, and may be confounded by differences in lifestyle factors between subjects. Using a comparison of runners and their non-runner control spouses, we conclude that habitual , high-intensity run training improves many aspects of the cardiovascular profile but does not reduce atherosclerosis measured by cIMT. These data are reassuring given recent reports that marathon running may intensify atherosclerotic disease progression in central and peripheral arteries, and suggest that exercise may reduce cardiovascular events by mechanisms independent of the atherosclerotic process.

CONTRIBUTORSHIP

BP, AZ, JC and PT planned the study and wrote the funding proposal. BP, AZ, JC, CT, AB, PD, PT and KB conducted study coordination, data collection and interepretation. BP, AZ, JC, MD and PT wrote the paper. All authors evaluated and revised the paper. BP submitted the paper and is responsible for the overall content as guarantor. The authors also gratefully acknowledge the research assistance provided by Lindsay and Judd Lorson, and William Roman and the logistical support provided by Dave McGillivray and the Boston Athletic Association; and Quest Diagnostics.

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COMPETING INTERESTS

Dr. Paul Thompson is a consultant for Astra Zenica International, Merck & Company, Inc., The Schering-Plough Corporation, Takeda Pharmaceutical Company Limited, Roche, and Genomas and is a member of the speaker's bureau for Merck & Company, Inc., Pfizer, Inc., Abbott Labs, Astra Zenica International, and The Schering-Plough Corporation.

DATA SHARING

There are no additional data available.

FIGURE LEGENDS

Figure 1. Relationships between age and left cIMT (A) and right cIMT (B) with data points represented for each individual subject and r^2 value shown for the entire sample. Solid line indicates regression line for runners; dashed line indicates regression line for controls.

Figure 2. Relationships between calculated Framingham Risk Score and left cIMT (A) and right cIMT (B) with data points represented for each individual subject and r^2 value shown for the entire sample. Solid line indicates regression line for runners; dashed line indicates regression line for controls.

Figure 3. Relationships between age and carotid augmentation pressure (A) and calculated Framingham Risk score and carotid augmentation pressure (B) with data points represented for each individual subject and r^2 value shown for the entire sample. Solid line indicates regression line for runners; dashed line indicates regression line for controls.

Figure 4. Relationship between age and carotid augmentation index with data points represented for each individual subject and r^2 value shown for the entire sample. Solid line indicates regression line for runners; dashed line indicates regression line for controls.

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Table 1. Subject Characteristics

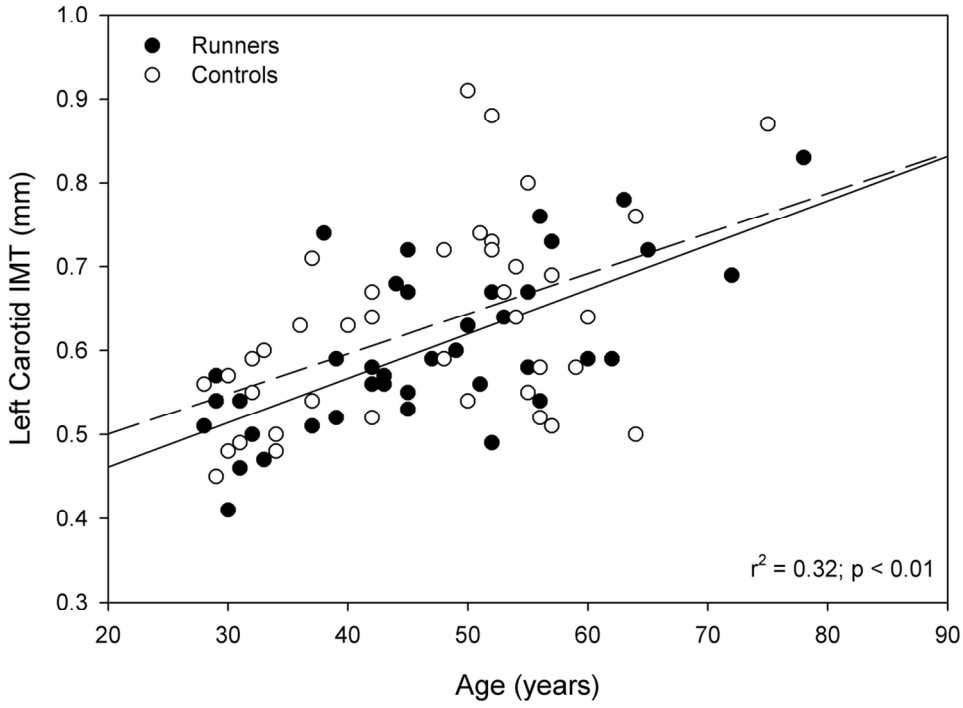
	Runners	Controls
Sample size (n)	42	42
Women (n)	21	21
Age (yrs)	46 ± 13	46 ± 12
Height (inches)	67 ± 5	67 ± 5
Weight (lbs)	149 ± 24*	170 ± 42
Meds (n)		
BP Lowering	1	5
NSAIDS	3	2
Aspirin	1	1
Cholesterol Lowering	2	4
Oral Contraceptives	5	2
Family History of CVD (n)	15	10
Race Time (Hours:minutes)	4:20 ± 0:47	--
Running Mileage	40 ± 16	--
Years Run	12 ± 10	--
Marathons Completed (n)	16 ± 30	--
Average Vig Ex/Day (hr)	2.0 ± 1.1*	0.6 ± 0.6
Average Mod Ex/Day (hr)	3.9 ± 2.2	3.2 ± 2.7
Block Fruit (pts)	18.7 ± 4.2	16.8 ± 4.5
Block Meat (pts)	11.5 ± 5.4	13.1 ± 5.8

BP = Blood pressure; NSAIDS = non-steroidal anti-inflammatories; CVD = cardiovascular disease; Vig Ex = Vigorous Exercise; Mod Ex = Moderate Exercise

Table 2. Cardiovascular Risk Factors

	Runners	Controls
Left cIMT (mm)	0.60 ± 0.09	0.62 ± 0.11
Right cIMT (mm)	0.60 ± 0.11	0.59 ± 0.10
SBP (mmHg)	130 ± 18	127 ± 17
DBP (mmHg)	76 ± 9	75 ± 10
HR (bpm)	57 ± 11*	69 ± 12
BMI (kg/m^2)	24 ± 4*	27 ± 5
Framingham Risk (pts)	3 ± 4	3 ± 3
hsCRP	0.6 ± 0.5*	1.6 ± 1.9
Total-C (mg/dL)	181 ± 29	188 ± 32
Non-HDL-C (mg/dL)	114 ± 31*	131 ± 32
HDL-C (mg/dL)	68 ± 18*	58 ± 16
LDL-C (mg/dL)	99 ± 27	110 ± 28
Triglycerides (mg/dL)	76 ± 29*	103 ± 58
Central SBP (mmHg)	130 ± 18	127 ± 17
Carotid AP (mmHg)	11 ± 8	10 ± 6
AI@HR75 (%)	14 ± 11	20 ± 11

cIMT = carotid intima medial thickness; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; BMI = body mass index; hsCRP = high sensitivity C reactive protein; C = cholesterol; HDL = high density lipoprotein; LDL = low density lipoprotein; SBP = Systolic Blood Pressure; AP = augmentation pressure; AI@HR75 = Augmentation Index at heart rate at 75 bpm.



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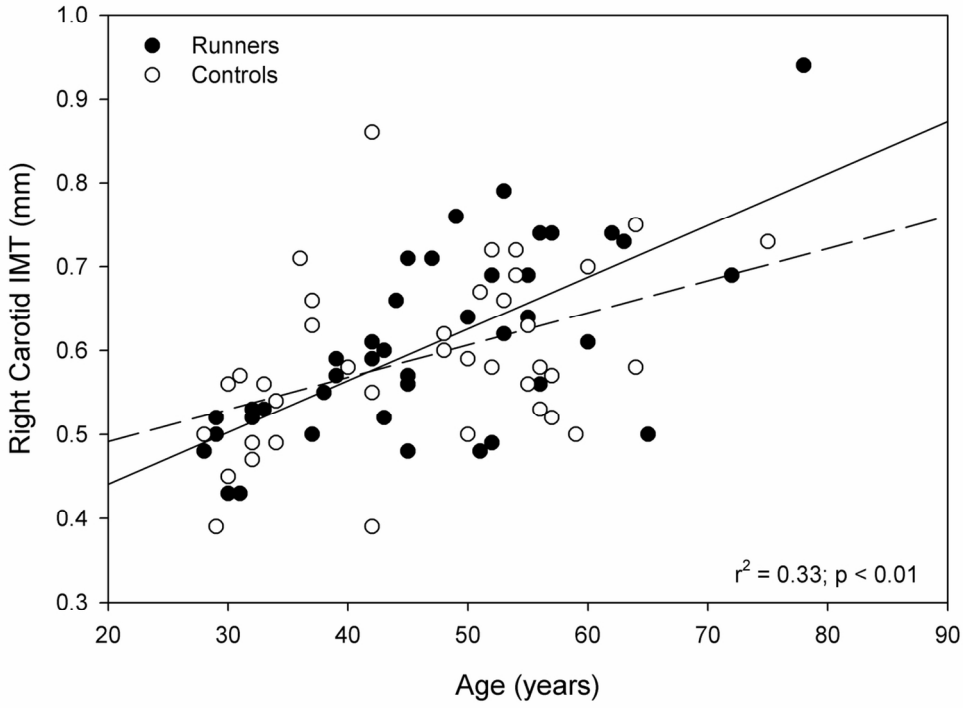

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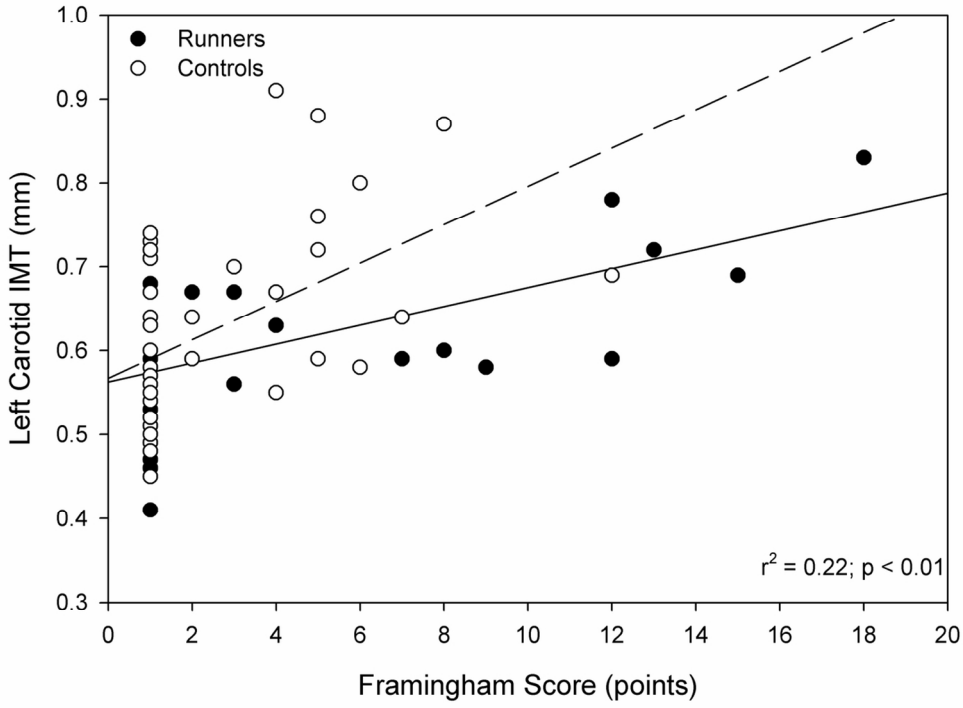

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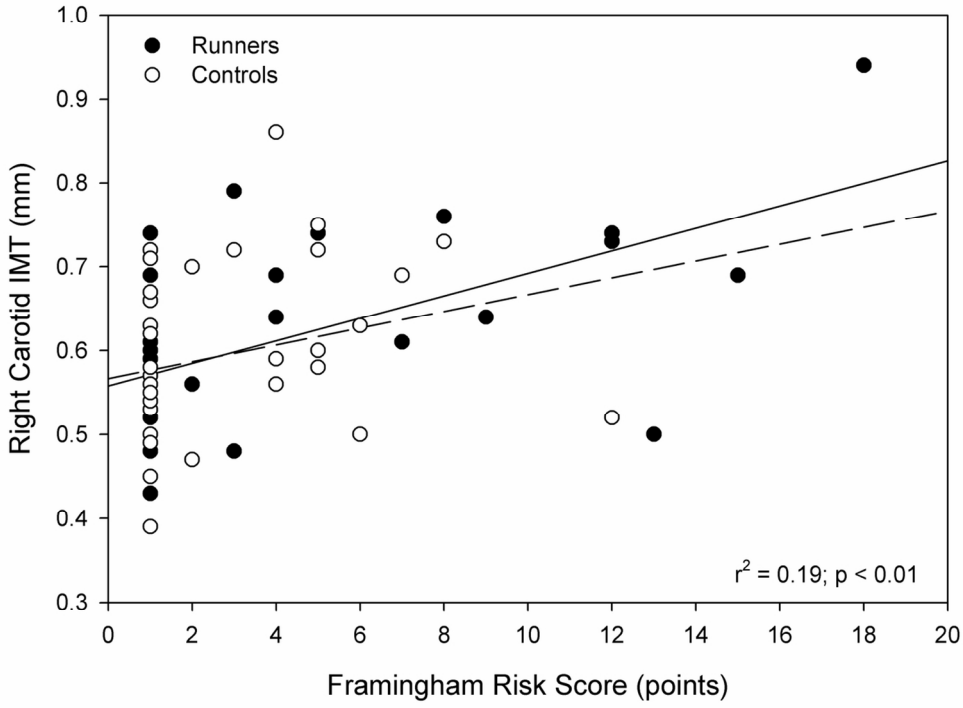

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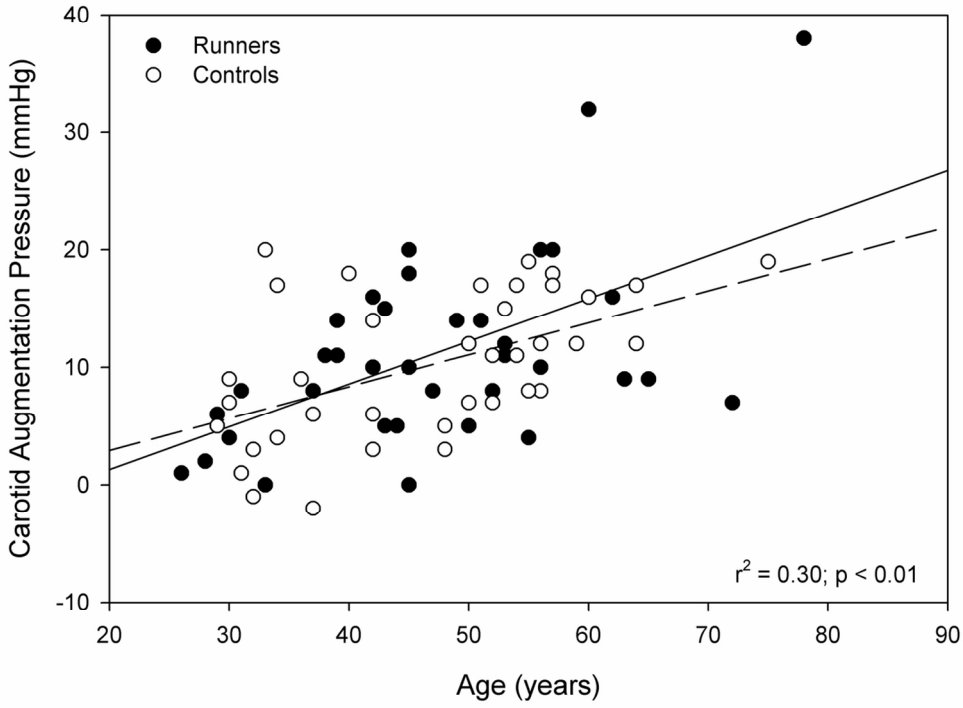

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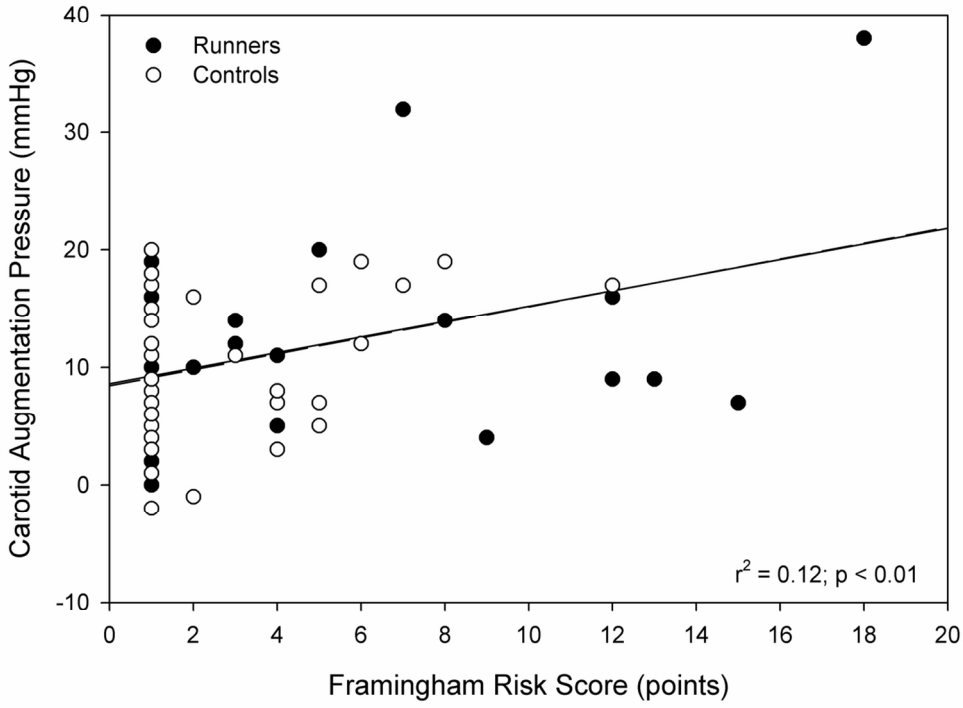

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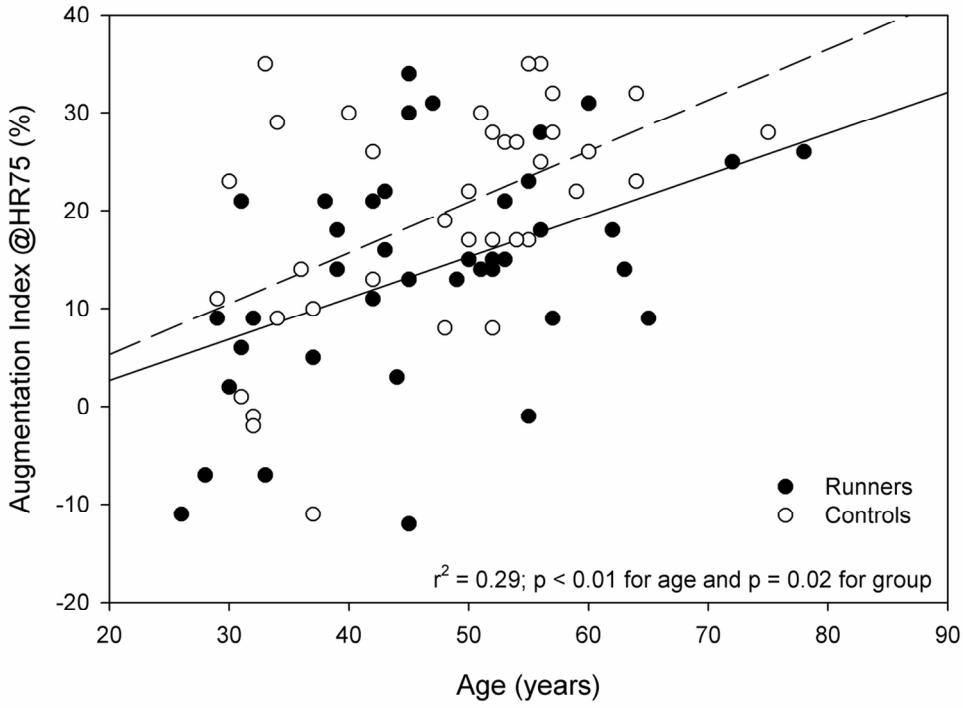

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses Page 5
Methods		
Study design	4	Present key elements of study design early in the paper Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants Page 5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 7
Bias	9	Describe any efforts to address potential sources of bias Page 5
Study size	10	Explain how the study size was arrived at Page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Page 7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
Page 7		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
Page 7		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram

Descriptive data Page 7	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data Page 7	15*	Report numbers of outcome events or summary measures
Main results Page 8	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses Page 8	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results Page 8	18	Summarise key results with reference to study objectives
Limitations Page 10	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation Page 9	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability Page 10	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding Page 11	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.