

Letter to the Editor

Physical activity, fitness, and vascular health in patients with asthma

To the Editor:

Patients with asthma are at an increased risk of cardiovascular disease (CVD),¹ and increased systemic inflammation associated with asthma may play a role. High levels of the proinflammatory cytokines IL-6, C-reactive protein, and tumor necrosis factor- α are elevated in asthma, and all are associated with increased CVD risk.^{2,3} Reduced endothelial vasodilation is seen in early stages of CVD development and is predictive of CVD.⁴ Patients with asthma have reduced endothelial function and increased arterial stiffness than do those without asthma.^{5,6} Systemic inflammation impairs endothelial function⁷ and increases arterial stiffness,⁸ but it is unknown whether there is a connection between systemic inflammation, vascular function, and arterial stiffness in subjects with asthma. Importantly, patients with asthma are usually more sedentary than their age-matched counterparts,⁹ and inactivity has been linked to increased inflammation, impaired vascular function, and increased CVD risk.¹⁰ Accordingly, we evaluated parameters of vascular function and systemic inflammation in patients with and without asthma matched for physical activity and aerobic fitness. We hypothesized that those with asthma would be associated with higher systemic inflammation, impaired endothelial function, and increased arterial stiffness as compared with controls even when matched for physical activity and aerobic fitness.

For complete methodology, see this article's [Methods](#) section in the Online Repository at www.jacionline.org. Briefly, patients with asthma (18-45 years, $n = 16$) with a body mass index of 30 kg/m² or less were recruited and compared with age-, body mass index-, physical activity-, and fitness-matched control subjects ($n = 16$) without asthma. Asthma diagnosis was based on history and 1) 12% or more and 200 mL improvement in FEV₁ postbronchodilator, 2) a positive methacholine challenge ($PC_{20} \leq 4$ mg/mL), or 3) 10% or more decrease in FEV₁ after an exercise challenge. Controls demonstrated negative responses to all the 3 tests described above. A cardiopulmonary exercise test was performed to determine aerobic fitness ($\dot{V}O_{2max}$). Physical activity was quantified as the number of steps taken over 3 days by a physical activity monitor. Vascular function was evaluated by flow-mediated dilation (FMD) adjusted for shear stress, and arterial stiffness was evaluated by the pulse wave velocity (PWV) between the radial and the carotid arteries using applanation tonometry. A blood sample was taken for analysis of systemic inflammatory markers (ie, IL-6, C-reactive protein, and tumor necrosis factor- α), fasting glucose, and cholesterol levels.

The Asthma Control Questionnaire indicated that patients with asthma were within the ranges of controlled to partly controlled asthma. There were no between-group differences in fraction of exhaled nitric oxide, postbronchodilator FEV₁, indices of blood pressure, fasting glucose, lipid profiles, or systemic inflammatory markers (see [Table I](#)). Although there were no differences in endothelial function (FMD) or microvascular function (velocity time

TABLE I. Subjects' characteristics

Characteristic	Control	Asthma	P value (2-tailed)
Sample size, n (male/female)	16 (8/8)	16 (10/6)	.72
Age (y)	26.6 $\pm$ 5.2	27.8 $\pm$ 6.1	.58
BMI (kg/m ²)	24.7 $\pm$ 3.5	24.6 $\pm$ 4.6	.96
FEV ₁ prebronchodilator (% predicted)	96.3 $\pm$ 12.1	81.3 $\pm$ 15.1	.004
FEV ₁ postbronchodilator (% predicted)	100.9 $\pm$ 13.2	91.6 $\pm$ 12.6	.051
FENO (ppb)	17.9 $\pm$ 8.5	37.3 $\pm$ 40.9	.16
Asthma Control Questionnaire score	0.1 $\pm$ 0.2	1.0 $\pm$ 0.4	<.001
Allergies (% yes)	18.8	57.1	.03
SABA usage (%)	0.0	56.3	<.001
ICS usage (%)	0.0	18.8	<.001
Combination ICS + LABA usage (%)	0.0	43.8	<.001
Physical activity, steps/d	10,711 $\pm$ 2,675	11,125 $\pm$ 5,487	.79
Fitness (relative $\dot{V}O_{2max}$) (mL/kg/min % predicted)	106.1 $\pm$ 15.9	97.1 $\pm$ 23.3	.21
Mean arterial pressure (mmHg)	79 $\pm$ 5	82 $\pm$ 10	.34
Heart rate (bpm)	55.7 $\pm$ 5.8	59.3 $\pm$ 6.0	.10
Total cholesterol (mmol/L)	3.7 $\pm$ 0.9	3.9 $\pm$ 1.4	.86
HDL (mmol/L)	1.4 $\pm$ 0.2	1.4 $\pm$ 0.4	.92
Fasting glucose (mmol/L)	3.9 $\pm$ 0.4	3.9 $\pm$ 0.4	.81
CRP (mg/L)	2.3 $\pm$ 3.83	3.6 $\pm$ 3.5	.46
IL-6 (pg/mL)	8.6 $\pm$ 5.9	6.9 $\pm$ 3.5	.35
TNF- α (pg/mL)	16.5 $\pm$ 5.1	16.3 $\pm$ 2.8	.91

Values are mean $\pm$ SD unless indicated otherwise.

BMI, Body mass index; bpm, beats per minute; CRP, C-reactive protein; FENO, fraction of exhaled nitric oxide; HDL, high-density lipoprotein; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; SABA, short-acting beta-agonist; TNF- α , tumor necrosis factor- α ; $\dot{V}O_2$, rate of oxygen consumption.

integral) between subjects with and without asthma, subjects with asthma had significantly higher arterial stiffness than did those without asthma ([Fig 1](#)). There was no relationship between FMD and markers of systemic inflammation in asthma (see [Fig E1, A-C](#), in this article's Online Repository at www.jacionline.org); however, there was a strong positive correlation between PWV and IL-6 in subjects with asthma, but no associations were observed between PWV and tumor necrosis factor- α or C-reactive protein (see [Fig E1, E and F](#)).

When matched for age, body mass index, physical activity, and aerobic fitness, those with asthma and controls had similar endothelial function, microvascular function, and systemic inflammation. Those with asthma had significantly higher arterial stiffness than did those without asthma, suggesting that structural changes within the vessel walls that are independent of physical activity, aerobic fitness, and inflammation occur in asthma.

Previous work found that as compared with controls, those with asthma have reduced vascular function⁶ and increased arterial stiffness.⁵ However, these studies did not report fitness or physical activity levels, and it is likely that those with asthma were less active.⁹ As a result, subjects with asthma would probably have exhibited lower fitness and impaired vascular health. In addition, previous work⁶ had not normalized vascular reactivity to its

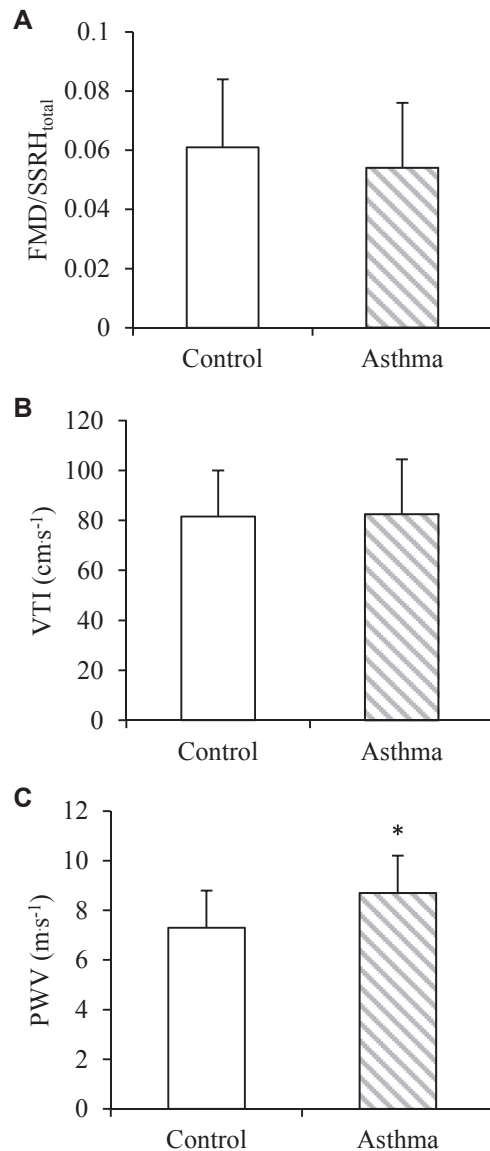


FIG 1. Endothelial function (A), microvascular function (B), and arterial stiffness (C) among controls and patients with asthma. Asterisk indicates $P < .05$ between groups. $SSRH_{total}$, Total shear stress after reactive hyperemia; VTI, velocity time integral.

stimulus (ie, shear stress). Our findings indicate that when matched for fitness or physical activity, those with asthma do not appear to have reduced vascular function as compared with healthy controls. However, the increase in arterial stiffness in those with asthma is related to lung disease, and not secondary to reduced physical activity or fitness.

Although increased levels of systemic inflammation are known to adversely affect vascular function and arterial stiffness,^{7,8} systemic inflammation was similar in both those with asthma and controls. These findings indicate that the increase in PWV in those with asthma relative to controls occurred independent of systemic inflammation. There was an association between IL-6 and arterial stiffness within those with asthma, suggesting that systemic inflammation may be related to arterial stiffness in those with asthma; however, it does not explain the elevation in PWV relative to controls.

All subjects in the present study were carefully screened, and it could be argued that these stringent inclusion criteria may have resulted in a sample inadequate to detect between-group differences in FMD. Our study was powered to detect a 10% difference in FMD between those with asthma and controls,⁶ corresponding to a large increase in the relative risk of CVD (for more details, see this article's Online Repository at www.jacionline.org). More importantly, the mean value for vascular function between those with asthma and controls was very similar, and a power calculation indicates that 340 subjects would have been required to detect a difference, which would have been well below any clinical significance. Beta agonists may modify sympathetic nerve activity, which could affect PWV and may explain the difference observed between those with asthma and controls. In the present study, all subjects with asthma withheld beta agonists for 12 hours before testing, and thus acute effects were controlled; however, chronic effects of asthma medication on vascular health are mostly still unknown. Furthermore, the age criteria in the present study did not allow for the evaluation of the influence of age or asthma duration on vascular health and further research is needed in this area.

In conclusion, stiffening of the systemic arteries appears to occur independently of physical activity, inflammation, and fitness in those with asthma. However, endothelial function and systemic inflammation are similar between physical activity and fitness-matched subjects with and without asthma, suggesting that mild controlled asthma alone does not contribute to increased systemic inflammation and/or impaired vascular function and that previous results showing impaired endothelial function and systemic inflammation in those with asthma may be explained by differences in baseline fitness and/or physical activity.

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REFERENCES

- Iribarren C, Tolstykh IV, Miller MK, Sobel E, Eisner MD. Adult asthma and risk of coronary heart disease, cerebrovascular disease, and heart failure: a prospective study of 2 matched cohorts. *Am J Epidemiol* 2012;176:1014-24.
- Ridker PM, Rifai N, Pfeffer M, Sacks F, Lepage S, Braunwald E. Elevation of tumor necrosis factor- α and increased risk of recurrent coronary events after myocardial infarction. *Circulation* 2000;101:2149-53.

3. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation* 2000;101:1767-72.
4. Yeboah J, Folsom AR, Burke GL, Johnson C, Polak JF, Post W, et al. Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study: the multi-ethnic study of atherosclerosis. *Circulation* 2009;120:502-9.
5. Sun WX, Jin D, Li Y, Wang RT. Increased arterial stiffness in stable and severe asthma. *Respir Med* 2014;108:57-62.
6. Yildiz P, Oflaz H, Cine N, Gencallac H, Erginel-Unaltuna N, Yildiz A, et al. Endothelial dysfunction in patients with asthma: the role of polymorphisms of ACE and endothelial NOS genes. *J Asthma* 2004;41:159-66.
7. Hingorani AD, Cross J, Kharbanda RK, Mullen MJ, Bhagat K, Taylor M, et al. Acute systemic inflammation impairs endothelium-dependent dilatation in humans. *Circulation* 2000;102:994-9.
8. Vlachopoulos C, Dima I, Aznaouridis K, Vasiliadou C, Ioakeimidis N, Aggeli C, et al. Acute systemic inflammation increases arterial stiffness and decreases wave reflections in healthy individuals. *Circulation* 2005;112:2193-200.
9. Teramoto M, Moonie S. Physical activity participation among adult Nevadans with self-reported asthma. *J Asthma* 2011;48:517-22.
10. Williams PT. Physical fitness and activity as separate heart disease risk factors: a meta-analysis. *Med Sci Sports Exerc* 2001;33:754-61.

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METHODS

This study (protocol no. Pro00029773) was approved by the University of Alberta Health Research Ethics Board. Written consent was obtained from all subjects before participation in the study.

Subjects

Men and women with asthma ($n = 16$) between the ages of 18 and 45 years and with a body mass index of 30 kg/m^2 or less were recruited from the University of Alberta Asthma Clinic and The Lung Health Clinic, Edmonton, Alberta, Canada. Asthma diagnosis was based on history of asthma symptoms such as recurrent episodes of wheezing, chest tightness, shortness of breath, and 1) 12% or less and 200 mL improvement in FEV_1 postbronchodilator,^{E1,E2} 2) a positive methacholine challenge ($\text{PC}_{20} \leq 4 \text{ mg/mL}^2$), or 3) 10% or more decrease in FEV_1 after an exercise challenge.^{E2,E3} Asthma control was evaluated according to the Asthma Control Questionnaire^{E4,E5} at the time of the first visit and only those with controlled (Asthma Control Questionnaire score of <0.75) and partly controlled (Asthma Control Questionnaire score of 0.75 – 1.5) asthma were included. Age, body mass index, and physical activity/fitness-matched control subjects ($n = 16$) without asthma (asymptomatic and as demonstrated by negative responses to all 3 the tests described above) were recruited from the general population. Subjects were excluded if demonstrating the following cardiovascular risk factors: hypertension (defined as resting systolic blood pressure of 140 mmHg or more and/or diastolic blood pressure of 90 mmHg or more),^{E6} a family history of sudden cardiac death or known coronary heart disease, elevated cholesterol levels (measured with CardioCheck capillary blood analyzer, Chek Diagnostics, Indianapolis, Ind),^{E7,E8} diabetes or impaired fasting glucose, smoking history (current smokers or persons who quit smoking within <6 months were excluded),^{E6} or 1 or more reason(s) to withhold from physical activity according to the Physical Activity Readiness Questionnaire (PAR-Q) and You Questionnaire.^{E7} Because coexisting allergies do not increase the risk of CVD in asthma^{E9} but may influence the systemic inflammatory profile,^{E10,E11} both atopic and nonatopic subjects were recruited and previously known allergies noted. Fractions of exhaled nitric oxide (NIOX MINO, Aerocrine, Inc, Solna, Sweden) were used for the evaluation of pulmonary inflammation, and the risk of obstructive sleep apnea was defined as having 3 or more risk factors occurring on the STOP-Bang questionnaire.^{E12,E13}

Measurements

Aerobic fitness. A graded cardiopulmonary exercise test was performed to determine the rate of oxygen consumption at maximal exercise ($\dot{V}\text{O}_{2\text{max}}$). The test was performed on a cycle ergometer (Ergoselect 200, Ergoline, Bitz, Germany) at incremental stages of 25 W until exhaustion. Breath-by-breath analysis of pulmonary gases was performed throughout the test using the Vmax Metabolic Cart (CareFusion, Yorba Linda, Calif). The subjects were asked to rate their level of perceived exertion at 2-minute intervals during the test, expressed on the modified Borg scale from 1 (nothing at all) to 10 (maximal). The highest $\dot{V}\text{O}_2$ reading (30 seconds time average) was reported as $\dot{V}\text{O}_{2\text{max}}$ as a measurement of cardiopulmonary fitness.^{E14}

Physical activity. Physical activity was quantified as the number of steps taken and energy expenditure through the use of physical activity monitors (biaxial accelerometers, SenseWear Pro3 Armband, Bodymedia, Milan, Italy). SenseWear Pro accelerometers have previously been shown to accurately measure energy expenditure^{E15,E16} and have been used in research with patients with respiratory diseases.^{E17} The subjects were instructed to wear the activity monitors on the back of their dominant upper arm for the entire day for a total of 3 days, preferably 2 weekdays and 1 day of the weekend. Data from the armbands were analyzed using SenseWear software (version 7.0.0.2378, Bodymedia).

Endothelial function. All endothelial function and arterial stiffness data were collected at the same time of day in the morning after a 12-hour fasting period.^{E18,E19} When applicable, the subjects were asked to withhold any long-acting beta agonists and/or corticosteroid medications for a minimum of 48 hours before the test and short-acting beta agonists for 12 hours before the test. No subjects were treated for medical conditions other than asthma, and decongestants were not taken within days before the study. The endothelial function of the brachial artery was evaluated at room temperature after 10 minutes of rest in the supine position using ultrasound imaging (8L-RS 4.0-13.0MHz probe, Vivid Q, GE Healthcare, Mississauga, Ontario, Canada). Baseline diameter of the brachial artery was established, and the blood flow of the forearm was subsequently occluded distally of the measuring site for a duration of 5 minutes. The blood velocity and the brachial diameter were monitored for 20 seconds before and 3 minutes after cuff-release, and later analyzed offline (Medical Imaging Applications, LLC, Coralville, Iowa; EchoPAC PC software, version 110, GE Healthcare, Horten, Norway). Microvascular function was evaluated as the velocity time integral (cm/s) envelope of the first heartbeat of reactive hyperemia.^{E20} The total shear stress after reactive hyperemia was calculated as $8 \times \text{mean velocity until peak FMD}/(\text{baseline diameter}/10)$.^{E18} All FMD tests were done by the same person. Changes within the vessel diameters were evaluated by 2 independent investigators. The interinterpreter correlation coefficients for baseline, peak, and peak % baseline diameter were $r = 0.96$, 0.97 , and 0.72 , respectively.

Arterial stiffness. Arterial stiffness was evaluated by the PWV between the radial and the carotid arteries using applanation tonometry (Mikro-tip Catheter Transducers model SPT-301, Millar Instruments, Inc, Houston, Texas). The carotid and radial pulses were obtained after 10 minutes of supine rest at room temperature, whereby PWV was recorded simultaneously over the 2 measuring sites. Approximately 30 waveforms were recorded from each subject, and 10 consecutive waveforms were selected for analysis (LabChart version 7.3.5, ADInstruments, New South Wales, Australia). The distance between measuring points was divided by the average difference in time between corresponding carotid-radial waveforms, as per guidelines.^{E21}

Blood collection. Blood was collected via an antecubital venipuncture immediately after the vascular function test. Once collected, resting glucose and cholesterol levels were measured immediately, and the blood was then allowed to clot at room temperature for a minimum of 30 minutes before being centrifuged at $1000g$ for 10 minutes at 4°C . Aliquots were outsourced to Eve Technologies (Calgary, Alberta, Canada) for analysis of inflammatory markers (ie, IL-6, C-reactive protein, and tumor necrosis factor- α).

Statistical analysis

Data are presented as mean $\pm$ SD unless otherwise stated. For all inferential analyses, the probability of type I error was set at 0.05. Subject characteristics and vascular parameters were compared between those with asthma and controls using 2-tailed independent samples t tests. Binomial variables were compared between those with asthma and controls using the chi-square test. The relationships between serum levels of tumor necrosis factor- α , IL-6, and C-reactive protein, and FMD/total shear stress after reactive hyperemia and PWV were evaluated in those with asthma using the Pearson product-moment correlation coefficient (r). Based on previous studies,^{E22} a sample size of 16 in each group was sufficient to detect a 10% difference in FMD between those with asthma and controls, corresponding to a more than 50% increase in the relative risk of CVD^{E23} ($\alpha = 0.05$; $\beta = 0.8$). All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS Statistics, IBM, version 20.0, Armonk, NY).

REFERENCES

- E1. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31:143-78.
- E2. Loughheed MD, Leniere C, Ducharme FM, Licskai C, Dell SD, Rowe BH, et al. Canadian Thoracic Society 2012 guideline update: diagnosis and management of asthma in preschoolers, children and adults: executive summary. *Can Respir J* 2012;19:e81-8.
- E3. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med* 2000;161:309-29.
- E4. Juniper EF, Bousquet J, Abetz L, Bateman ED. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respir Med* 2006;100:616-21.
- E5. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902-7.
- E6. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics-2012 update: a report from the American Heart Association. *Circulation* 2012;125:e2-220.
- E7. The American College of Sport Medicine, American College of Sport medicine's guideline for exercise testing and prescription; Preparticipation Health Screening; 2009; Chapter 2; Page 24.
- E8. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-97.
- E9. Iribarren C, Tolstykh IV, Miller MK, Sobel E, Eisner MD. Adult asthma and risk of coronary heart disease, cerebrovascular disease, and heart failure: a prospective study of 2 matched cohorts. *Am J Epidemiol* 2012;176:1014-24.
- E10. Wood LG, Baines KJ, Fu J, Scott HA, Gibson PG. The neutrophilic inflammatory phenotype is associated with systemic inflammation in asthma. *Chest* 2012;142:86-93.
- E11. Olafsdottir IS, Gislason T, Thjodleifsson B, Olafsson I, Gislason D, Jogi R, et al. C reactive protein levels are increased in non-allergic but not allergic asthma: a multicentre epidemiological study. *Thorax* 2005;60:451-4.
- E12. Chung F, Subramanyam R, Liao P, Sasaki E, Shapiro C, Sun Y. High STOP-Bang score indicates a high probability of obstructive sleep apnoea. *Br J Anaesth* 2012;108:768-75.
- E13. Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S, et al. Stop questionnaire: a tool to screen patients for obstructive sleep apnea. *Anesthesiology* 2008;108:812-21.
- E14. Stickland MK, Butcher SJ, Marciniuk DD, Bhutani M. Assessing exercise limitation using cardiopulmonary exercise testing. *Pulm Med* 2012;2012:824091.
- E15. Johannsen DL, Calabro MA, Stewart J, Franke W, Rood JC, Welk GJ. Accuracy of armband monitors for measuring daily energy expenditure in healthy adults. *Med Sci Sports Exerc* 2010;42:2134-40.
- E16. Welk GJ, McClain JJ, Eisenmann JC, Wickel EE. Field validation of the MTI Actigraph and BodyMedia armband monitor using the IDEEA monitor. *Obesity (Silver Spring)* 2007;15:918-28.
- E17. Pitta F, Takaki MY, Oliveira NH, Sant'anna TJ, Fontana AD, Kovelis D, et al. Relationship between pulmonary function and physical activity in daily life in patients with COPD. *Respir Med* 2008;102:1203-7.
- E18. Harris RA, Nishiyama SK, Wray DW, Richardson RS. Ultrasound assessment of flow-mediated dilation. *Hypertension* 2010;55:1075-85.
- E19. Thijssen DH, Black MA, Pyke KE, Padilla J, Atkinson G, Harris RA, et al. Assessment of flow-mediated dilation in humans: a methodological and physiological guideline. *Am J Physiol Heart Circ Physiol* 2011;300:H2-12.
- E20. Philpott AC, Lonn E, Title LM, Verma S, Buithieu J, Charbonneau F, et al. Comparison of new measures of vascular function to flow mediated dilatation as a measure of cardiovascular risk factors. *Am J Cardiol* 2009;103:1610-5.
- E21. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006;27:2588-605.
- E22. Yildiz P, Oflaz H, Cine N, Gencchallac H, Erginel-Unaltuna N, Yildiz A, et al. Endothelial dysfunction in patients with asthma: the role of polymorphisms of ACE and endothelial NOS genes. *J Asthma* 2004;41:159-66.
- E23. Green DJ, Jones H, Thijssen D, Cable NT, Atkinson G. Flow-mediated dilation and cardiovascular event prediction: does nitric oxide matter? *Hypertension* 2011;57:363-9.

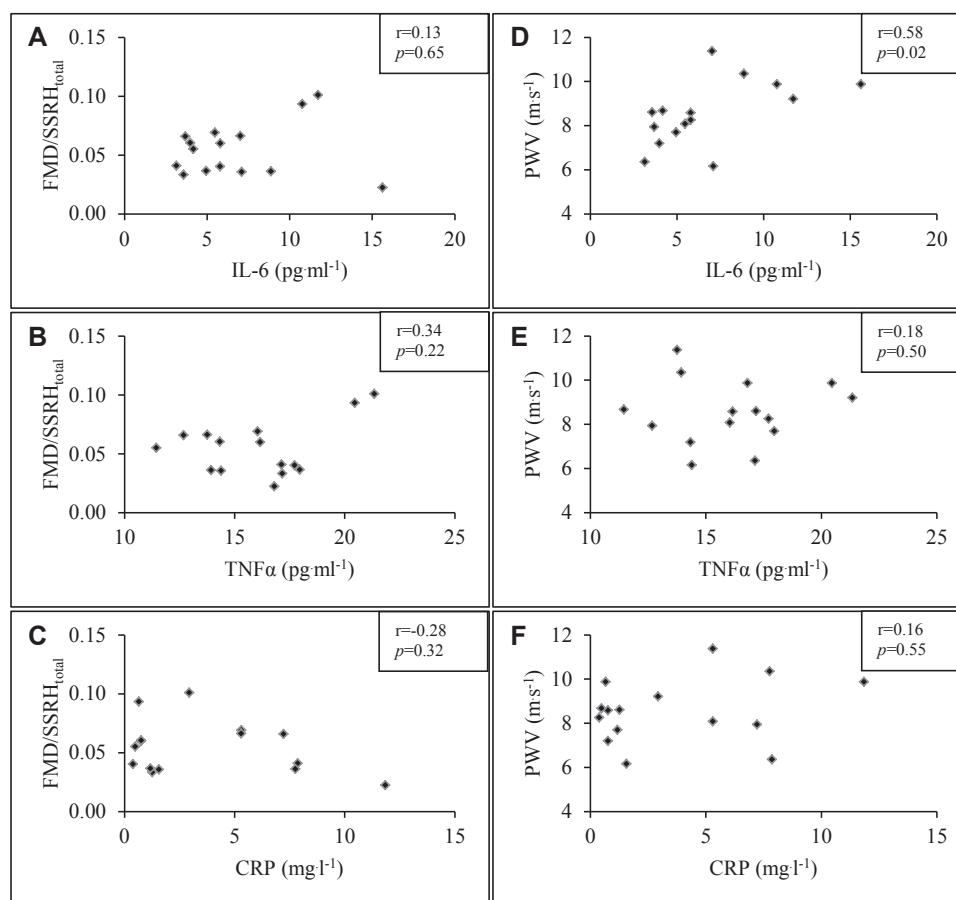


FIG E1. Relationship between endothelial function and systemic inflammation—FMD/SSRH_{total} vs (A) IL-6, $P = .65$, (B) TNF- α , $P = .22$, and (C) CRP, $P = .32$ —and arterial stiffness and systemic inflammation—PWV vs. (D) IL-6, $r = 0.57$, $P < .05$, (E) TNF = α , $P = .50$, and (F) CRP, $P = .55$ —in subjects with asthma. CRP, C-reactive protein; SSRH_{total}, total shear stress after reactive hyperemia; TNF- α , tumor necrosis factor-alpha.