Metabolic Predictors of Change in Vascular Function

Prospective Associations From a Community-Based Cohort

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Abstract—Vascular function varies with age because of physiological and pathological factors. We examined relations of longitudinal change in vascular function with change in metabolic traits. Longitudinal changes in vascular function and metabolic traits were examined in 5779 participants (mean age, 49.8±14.5 years; 54% women) who attended sequential examinations of the Framingham Offspring, Third Generation, and Omni-1 and Omni-2 cohorts. Multivariable regression analysis related changes in vascular measures (dependent variables), including carotid-femoral pulse wave velocity (CFPWV), forward pressure wave amplitude, characteristic impedance, central pulse pressure, and mean arterial pressure (MAP), with change in body mass index, fasting total:high-density lipoprotein cholesterol ratio, serum triglycerides, and blood glucose. Analyses accounted for baseline value of each vascular and metabolic measure, MAP change, and multiple comparisons. On follow-up (mean, 5.9±0.6 years), aortic stiffness (CFPWV, 0.2±1.6 m/s), and pressure pulsatility (forward pressure wave, 1.2±12.4 mm Hg; characteristic impedance, 23±73 dyne×sec/cm^5; central pulse pressure, 2.6±14.7 mm Hg; all P<0.0001) increased, whereas MAP fell (−3±10 mm Hg; P<0.0001). Worsening of each metabolic trait was associated with increases in CFPWV and MAP (P<0.0001 for all associations) and an increase in MAP was associated with an increase in CFPWV. Overall, worsening metabolic traits were associated with worsening aortic stiffness and MAP. Opposite net change in aortic stiffness and MAP suggests that factors other than distending pressure contributed to the observed increase in aortic stiffness. Change in metabolic traits explained a greater proportion of the change in CFPWV and MAP than baseline metabolic values. **(*Hypertension*. 2018;71:237-242. DOI: 10.1161/HYPERTENSIONAHA.117.10054.)** ● **Online Data Supplement**

Key Words: arterial pressure ■ blood glucose ■ body mass index ■ triglycerides ■ vascular stiffness

Arterial stiffness measures predict the onset of hypertension and incident cardiovascular disease (CVD) events.[1–5] Cross-sectional correlates of vascular stiffness include age, sex, weight, blood pressure, height, and metabolic features like fasting glucose and lipid levels.[6] Our previous work demonstrated strong, nonlinear relations between age and aortic stiffness measures, suggesting that aortic stiffness increases over time, particularly after midlife.[7] Prior work has shown that age-related trends in average values for risk factors, such as blood pressure, may include effects from aging itself, age-related changes in other risk factor levels, birth cohort effects, or other factors.[8–10] CVD risk factors found to be associated with aging-related phenotypes in cross-sectional analyses can differ from observed associations in longitudinal analyses.[11] Therefore, we sought to assess the prospective associations of changes in large and small vessel function (as dependent variables) with changes in metabolic traits (as the independent variables) in a large community-based, multiethnic sample of middle-aged and older adults. Based on previously identified cross-sectional associations between metabolic risk factors and vascular function and between older age and worsening vascular function, we hypothesized that longitudinal worsening of metabolic traits would be associated with worsening of large and small vessel function.

Methods

Data, analytic methods, and study materials are available to other researchers through National Heart, Lung, and Blood Institute BioLINCC repository at https://biolincc.nhlbi.nih.gov/studies/framcohort/. The study sample consisted of participants in the Framingham Offspring, Omni 1, Third Generation, and Omni 2 cohorts, which have been described in detail.[12,13] Briefly, children of

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the Framingham Original cohort, and spouses of those children, were recruited beginning in 1971 (n=5124) into the Offspring cohort. To reflect the increased diversity of the Framingham community, the ethnic or racial minority Omni 1 cohort was recruited in 1994 (n=507). Participants who attended sequential Offspring examinations 8 and 9 (n=2224) or Omni 1 examinations 3 and 4 (n=254) were eligible for inclusion in the present analyses. Also included in our analysis are members of the Framingham Third Generation cohort (n=4095), comprised of the children of the Offspring cohort and the spouses of those children as well as a second minority cohort (Omni 2, n=410). Participants of the Third Generation or Omni 2 cohort who attended sequential examinations 1 and 2 (n=3411 and n=322, respectively) were also eligible, giving a total eligible sample of 6211 individuals. The Omni cohorts were comprised of black, Hispanic, and Asian individuals residing in the MetroWest Boston area. Of these 6211 participants, 432 individuals were excluded for missing tonometry data at either of the sequential examinations (Figure S1 in the online-only Data Supplement). The Boston University Medical Center institutional review board approved the study protocol and written informed consent was given by all participants.

Participants return to the Heart Study clinic approximately every 4 to 6 years for examinations that include standardized questionnaires focused on cardiometabolic disease and risk factors, physical examinations, including anthropometrics and a standardized protocol to measure seated blood pressure and assessment of standard CVD risk factors. Laboratory evaluation of standard CVD risk factors was performed on venous blood samples obtained after a 12 hour overnight fast at baseline and follow-up visits. Plasma cholesterol and triglyceride concentrations were measured by enzymatic methods, HDL-C (high-density lipoprotein cholesterol) was measured after dextran sulfate–magnesium precipitation of apolipoprotein B–containing lipoproteins, and blood glucose was measured using hexokinase reagent.

Applanation Tonometry

Participants underwent applanation tonometry in a supine position after 5 minutes of rest as described previously in detail.[6] Systolic and diastolic blood pressures were measured on the right arm using a semiautomated auscultatory method (Cardiovascular Engineering Inc, Norwood, MA). Tonometry waveforms were obtained from the right-sided carotid, brachial, radial, and femoral arteries by using a handheld custom tonometer. A caliper was used to measure the distance from the suprasternal notch to the femoral site and a fiberglass tape measure was used to measure from suprasternal notch to other sites. Waveform signals were digitized (1000 Hz) and then transferred to the core laboratory (Cardiovascular Engineering Inc, Norwood, MA), where analyses were performed blinded to all clinical data.

The R-wave of the ECG was used as the reference point to signal average waveforms and assess relative timing between pulse sites. Brachial cuff systolic and diastolic pressures were used to calibrate tonometry-derived signal-averaged brachial pressure waveforms. The brachial artery waveform was integrated to calculate mean arterial pressure (MAP). Assuming uniform diastolic and mean pressure in large arteries, brachial mean and diastolic pressures were used to calibrate the carotid waveform. The carotid waveform was used as a surrogate for central arterial pressure. Carotid-femoral transit distance was adjusted for parallel transmission by using the suprasternal notch as a fiducial point.[7] Carotid-femoral pulse wave velocity (CFPWV) was calculated by dividing the adjusted transit distance by the pulse transit time difference between carotid and femoral sites. Previous work has demonstrated that raw CFPWV values exhibit heteroscedasticity and skewness. Therefore, raw CFPWV was inverted (1/CFPWV) and then multiplied by −1000 to compute negative inverse CFPWV. Higher values of niCFPWV, which has units of ms/m, correspond to higher aortic stiffness. Central pulse pressure (CPP) was calculated as carotid systolic blood pressure−diastolic blood pressure. Forward pressure wave (FPW) amplitude was assessed by performing time domain wave separation analysis using central pressure and flow.[7] Characteristic impedance (Zc), which is the impedance to pulsatile flow during systole, was calculated in the time domain by dividing the pressure increase by the flow increase up to 95% of peak flow.[7]

Covariate Definitions

Prevalent CVD, as adjudicated by the Framingham end points review committee, included the presence of coronary heart disease (angina, coronary insufficiency, and myocardial infarction), cerebrovascular disease (stroke or transient ischemic attack), heart failure, or intermittent claudication. Hypertension was defined as a study physician-measured seated averaged arm blood pressure ≥140/90 mm Hg or current use of antihypertensive medications. Diabetes mellitus was defined as a fasting glucose concentration ≥126 mg/dL or the use of hypoglycemic medications. Body mass index (BMI) was treated as a continuous variable calculated as the body weight in kilograms divided by the square of height in meters. Heart rate was measured in beats per minute. Smoking was ascertained based on self-reported smoking of at least 1 cigarette per day within the year preceding the Heart Study examination. Treatment with lipid-lowering medications was also recorded.

Statistical Analyses

The primary exposures of interest (independent variables) were BMI, fasting plasma glucose, total:HDL-C ratio, and triglycerides (which were natural logarithm transformed to normalize their skewed distribution), modeled as the combination of baseline visit level and the change from baseline to follow-up visit, and entered as a paired set in all models. Additional covariates included age, age squared, sex, cohort, time elapsed between baseline and follow-up visit, baseline visit values for height (meters), heart rate, presence of hypertension, lipid-lowering therapy, prevalent CVD, smoking and diabetes mellitus, and the initial value for the vascular measure at the baseline examination. The primary outcome variables (dependent variables) were changes from baseline visit to follow-up visit for CFPWV, FPW, CPP, Zc, and MAP (separate model for each).

Generalized linear models were constructed for each of the outcome variables with primary exposures of interest and covariates noted above. Then baseline value and change in MAP were added to each of the models, except for the model with MAP as the outcome. We accounted for relatedness of participants by using generalized estimating equations.[14] Then for each hemodynamic change outcome variable, forward stepwise models were constructed by using the aforementioned base model and offering the paired baseline and change in metabolic measures as candidates for entry into the model. At this stage a sensitivity analysis was performed replacing glucose with fasting serum insulin concentration. The paired metabolic variables were retained if the P value for entry of the pair was <0.05.

Sex interaction terms were examined by including the product of sex and change in each of the metabolic variables as an additional term in the model. Age interaction terms were examined by dichotomizing (grouping) the combined cohort into individuals at or above the median age versus below the median age at the time of the baseline examination, and then adding a term representing the product of age group and change in each of the metabolic variables as an additional term in the model.

The change in model R^2 with the addition of the combination of significant baseline visit metabolic variables and the change in R^2 for the combination of change in metabolic variables was reported to assess the relative proportion of variance of vascular outcome change attributable to each respectively. Adjustment for 48 comparisons (5 dependent vascular outcomes and baseline or change in 4 metabolic independent variables and MAP) resulted in a threshold for statistical significance of P<0.05/48=0.001 for a 2-sided test. SAS 9.3 (Cary, NC) was used for all analyses.

Results

Baseline characteristics of the combined cohorts are presented in Table 1. The sample included 5779 individuals (54% women, 2.9% black, 3.2% Hispanic, and 2.5% Asian) with a broad age range (19 to 91 years) and a mean age of 49.8±14.5 years. On average, CFPWV, FPW, CPP, and Zc increased and MAP fell during a mean follow-up of 5.9±0.6 years (Table 2). During the same time period, BMI, triglycerides, and total:HDL-C ratio increased, whereas fasting glucose did not change (Table 2).

Table 1. Sample Characteristics at Baseline and Follow-Up (n=5779)

Characteristic	Baseline	Follow-Up
Age, y	49.8±14.5	55.7±14.3
Women, n (%)	3123 (54)	
Height, cm	169.1±9.6	
Weight, kg	78.2±18.0	79.7±18.5
Heart rate, bpm	61±10	63±10
Blood pressure lowering medicine, n (%)	1338 (23)	1817 (32)
Lipid-lowering medication, n (%)	1143 (20)	1727 (30)
Diabetes mellitus, n (%)	358 (6.2)	522 (9.0)
Smoker, n (%)	638 (11.0)	509 (8.8)
Prevalent cardiovascular disease, n (%)	276 (4.8)	418 (7.2)

All data are means±SD or counts and proportions as indicated.

Results of regression modeling of vascular change outcome measures onto baseline and change in metabolic independent variable pairs are shown in Table S1. Baseline BMI was associated with a decline in FPW, Zc, and CPP and an increase in MAP, but was not associated with change in CFPWV over time. An increase in BMI over time was associated with an increase in CFPWV and MAP. Baseline and change in serum glucose concentration, total:HDL-C ratio, and triglycerides were associated with a longitudinal increase in CFPWV and MAP. Baseline levels of glucose and triglycerides were associated with longitudinal increase in FPW. MAP at baseline and change in MAP were positively associated with increases in CFPWV, FPW, Zc, and CPP. Several other nominal associations that did not meet multiple comparison corrected significance threshold were also present.

Results of stepwise models are presented in Table 3. The models for CFPWV and FPW change retained associations with paired (baseline and change) levels of BMI, glucose, and triglycerides. The model for CPP change retained associations with baseline BMI and triglyceride, whereas Zc change retained baseline BMI and total:HDL-C ratio. The model for MAP change retained paired levels of BMI and triglycerides. When fasting glucose was replaced by fasting insulin level, baseline and change in insulin levels were not related to change in vascular measures at the corrected significance level (data not shown). The proportion of variance explained by the various stepwise models including all retained metabolic variables and covariates was modest, ranging from 0.6% to 3% across the various hemodynamic change outcomes. For CFPWV and MAP change, change in metabolic variables accounted for a higher proportion of the variance than did baseline visit metabolic values, whereas for FPW, Zc, and CPP the opposite was true. Effect modification by sex was present only for the relation between change in BMI and change in MAP. A longitudinal increase in BMI was associated with a larger longitudinal increase in MAP in men (0.75±0.11 mm Hg per kg/m^2; P=0.0002) than in women (0.36±0.09 mm Hg per kg/m^2, P<0.0001; interaction term, P=0.0002). Effect modification by age at or above the median versus below the median was not found for any cardiometabolic predictor model sets.

Discussion

In our multiethnic adult cohort spanning a broad age range, measures of aortic stiffness (CFPWV) and pressure pulsatility (FPW, Zc, and CPP) increased, whereas MAP fell between 2 examinations separated by ≈6 years. Changes in vascular measures were associated with baseline levels and change in several metabolic traits.[6] For example, changes in CFPWV and MAP were associated with changes in BMI, glucose, total:HDL-C ratio, and triglycerides. In contrast, changes in FPW, Zc, and CPP were associated with baseline cardiometabolic factors but were not related to change in these risk factors. Each of the aortic stiffness measures was related to baseline and change in MAP. Sex-based differences in associations were seen only for the relation of change in BMI with change in MAP, where the slope of the relation between BMI and MAP was steeper in men than in women. However, despite positive associations of MAP at baseline and change in MAP with increase in aortic stiffness and pulsatility measures over the observation period,

Table 2. Unadjusted Exposure and Hemodynamic Outcome Variables

Variable	Baseline	Follow-Up	Mean Change	Mean Change Per Year	P Value
Body mass index, kg/m^2	27.2±5.3	28.0±5.5	0.8±2.4	0.13±0.4	<0.0001
Fasting glucose, mg/dL	98.8±19.8	98.8±19.5	0.1±18.0	0.003±3.138	0.95
Total:HDL-C ratio	3.7±1.2	3.3±1.1	−0.4±0.9	−0.06±0.15	<0.0001
Log$_e$ triglycerides	4.6±0.5	4.6±0.5	0.01±0.4	0.002±0.071	0.03
CFPWV, m/s	8.1±2.7	8.3±2.8	0.2±1.6	0.04±0.28	<0.0001
niCFPWV, ms/m	−133.2±32.8	−130.7±32.9	2.7±17.8	0.46±3.05	<0.0001
FPW, mm Hg	48.4±13.8	49.6±14.1	1.2±12.4	0.21±2.12	<0.0001
Zc, dynes×sec/cm^5	197±73	220±87	23±73	3.87±12.62	<0.0001
Supine CPP, mm Hg	56.6±17.8	59.1±18.6	2.6±14.7	0.44±2.54	<0.0001
MAP, mm Hg	92.5±11.9	89.2±11.2	−3.3±10.4	−0.57±1.79	<0.0001

CFPWV indicates carotid-femoral pulse wave velocity; CPP, central pulse pressure; FPW, forward pulse wave amplitude; HDL-C, high-density lipoprotein cholesterol; MAP, mean arterial pressure; niCFPWV, negative inverse CFPWV (−1000/CFPWV); and Zc, characteristic impedance.

Table 3. Forward Stepwise Regression Model Results of Metabolic Variable Combinations on Change in Hemodynamic Outcomes

Metabolic Variables		Hemodynamic Outcome Variable				
Name	Timing	niCFPWV, ms/m	FPW, mm Hg	Zc, dyne×sec/cm^5	CPP, mm Hg	MAP, mm Hg
BMI, per 1 kg/m^2	Baseline	−0.07±0.05 (0.10)	−0.15±0.03 (<0.0001)*	−1.73±0.19 (<0.0001)*	−0.22±0.03 (<0.0001)*	0.10±0.02 (0.0001)*
	Change	0.31±0.09 (0.0009)*	−0.07±0.06 (0.25)	−0.48±0.39 (0.21)	−0.19±0.07 (0.008)	0.58±0.05 (<0.0001)*
Glucose, per 1 mg/dL	Baseline	0.06±0.02 (0.0004)*	0.04±0.01 (0.0002)*	0.22±0.07 (0.002)	0.04±0.01 (0.005)	…
	Change	0.07±0.01 (<0.0001)*	0.01±0.009 (0.16)	0.12±0.06 (0.04)	0.004±0.01 (0.70)	…
Total:HDL-C ratio, per 1 U	Baseline	…	…	3.39±0.91 (0.0002)*	…	…
	Change	…	…	2.80±1.14 (0.01)	…	…
Triglycerides, per 1 loge unit	Baseline	2.70±0.48 (<0.0001)*	1.42±0.33 (<0.0001)*	…	1.63±0.38 (<0.0001)*	1.45±0.28 (<0.0001)*
	Change	2.75±0.57 (<0.0001)*	0.54±0.38 (0.16)	…	0.30±0.44 (0.49)	2.27±0.33 (<0.0001)*
Covariates only model R^2		0.3579 (<0.0001)	0.3622 (<0.0001)	0.2457 (<0.0001)	0.4019 (<0.0001)	0.2733 (<0.0001)
Baseline metabolic variables partial R^2		0.002 (0.0008)	0.0054 (<0.0001)	0.0112 (<0.0001)	0.0063 (<0.0001)	0.0018 (0.0009)
Change metabolic variables partial R^2		0.0104 (<0.0001)	0.0005 (<0.0001)	0.0014 (<0.0001)	0.0007 (<0.0001)	0.0284 (<0.0001)
Total model R^2		0.3703 (<0.0001)	0.3681 (<0.0001)	0.2583 (<0.0001)	0.4089 (<0.0001)	0.3035 (<0.0001)

Regression estimates (change in native units per 1 native unit difference or change in independent variable), SE, and *P* values (in parentheses) for baseline and change of the metabolic predictors are reported, as well as the partial R^2 and *P* value in parentheses for the group covariates forced in to the group of significant metabolic variables at baseline, the group of change in metabolic variables. Because of skewed distribution, triglycerides were natural logarithm transformed. For each hemodynamic variable, only the independent metabolic variables found significant as a group (baseline and change) on forward stepwise regression after forced entry of covariates were included in the combined model and were retained in the model at *P* value <0.01. Covariates forced into each model include age, age squared, sex, cohort, time between exams, baseline height, heart rate, hypertension therapy, lipid therapy, prevalent CVD, smoking, and prevalent diabetes mellitus. The non-MAP models were additionally adjusted for baseline value and change in MAP. BMI indicates body mass index; CFPWV, carotid-femoral pulse wave velocity; CPP, central pulse pressure; FPW, forward pulse wave amplitude; HDL-C, high-density lipoprotein cholesterol; MAP, mean arterial pressure; niCFPWV, negative inverse CFPWV (−1000/CFPWV); and Zc, characteristic impedance.

*Results significant at a Bonferroni-corrected *P* value threshold, which for 48 possible tests is conservatively set to *P*<0.05/48=0.001.

aortic stiffness measures increased during the follow-up period, whereas MAP decreased. A functional change in aortic stiffness as a result of a change in distending pressure was unlikely to explain the concordant increases in aortic stiffness and pulsatility measures in light of the fall in MAP. Whereas metabolic traits were consistently associated with arterial measures, baseline and change in metabolic measures explained a small proportion (1% to 3%) of the variance in vascular change. Although most of the variance in vascular outcomes remain unexplained, for FPW, Zc, and CPP baseline metabolic variables explained more of the variance than change in metabolic traits, whereas for the key outcome CFPWV and MAP, change in metabolic traits predominated.

Previous work has shown a consistent association between baseline adiposity, as measured by weight, BMI, or waist circumference, and increase in CFPWV across age, sex, and race.[15–21] A study of younger adults between 20 and 40 years of age showed weight gain was associated with an increase in CFPWV, whereas another study of young to middle-aged adult men found that change in BMI did not predict change in CFPWV.[16,19] In our cohort, baseline BMI was not associated with change in CFPWV but increasing BMI was associated with an increase in CFPWV. Pleiotropic effects of adiposity include predisposition toward hyperglycemia, hypertriglyceridemia, diminished HDL-C, insulin resistance, diffuse fibrosis, altered neurohormonal axes, and volume retention.[22–30] This potent milieu may increase vessel distention, promote fibrosis in large and small blood vessels, and alter vascular tone. However, the longitudinal decline in FPW, Zc, and CPP in those with higher BMI at baseline and the lack of change in pulsatility measures with an increase in BMI over time contrasts strongly with the increase in MAP and CFPWV in those with an increase in BMI over time. The discordant pattern of change in stiffness and pulsatility measures suggests that factors other than fibrosis of the aortic wall may be involved in longitudinal remodeling of the aorta. CFPWV, as the gold-standard measure of aortic stiffness, is strongly dependent on aortic wall stiffness.[31] Zc is similarly dependent on aortic wall stiffness, but has in addition a strong inverse relation with aortic diameter.[1,32–34] The differing relations of CFPWV and Zc with BMI may therefore relate to remodeling of the diameter of the aorta with increasing BMI, which could simultaneously increase wall stiffness (CFPWV), because a larger aorta is under greater wall stress, and reduce impedance to pulsatile flow (Zc), because the greater lumen area can accommodate higher flows.

Our findings differ from previous work with respect to the relations of changes in glycemic measures with arterial function. Although most studies have shown that baseline glucose is not associated with change in aortic stiffness, one study demonstrated associations of glucose with vascular change only in men and a different study only in women.[15,16,18,19] No studies to date have demonstrated an association with change in glucose and change in aortic stiffness. Our data suggest baseline and change in glucose was associated with change in CFPWV and

change in MAP, although after entry into the same model with other traits, change in glucose no longer maintained relations with change in MAP. Associations of glycemia with change in CFPWV and MAP may be consistent with direct effects of glycemic regulatory mechanisms on vascular properties, direct effects of glucose or advanced glycation end products on the vasculature, or indirect effects of glycemia mediated by alterations in endothelial nitric oxide (NO) production.[35] In those affected by diabetes mellitus and insulin resistance, vascular dysfunction has been associated with decreased endothelial NO production, higher oxidative stress and increased accumulation of advanced glycation end products and expression of receptor of advanced glycation end products.[36,37] Circulating advanced glycation end products disrupt cell-extracellular matrix and matrix–matrix interactions and increase collagen cross-linking, potentially leading to an increase in vascular stiffness.[38,39]

Similar to glycemia, previous studies on lipid associations to vascular function have been equivocal, with some demonstrating baseline HDL and triglyceride values were associated with aortic stiffness, whereas others showed no association. One study showed an association between triglycerides and vascular function only in men.[15,16,18,19] No prior studies have demonstrated relations of lipid traits with change in vascular function. Our observations provide some evidence of longitudinal associations between lipids and stiffness measures although several associations were attenuated after inclusion of additional metabolic variables in a single model. The differences in our study versus previous investigations are likely based on the larger sample size, adult age range, including pre- and postmenopausal women, and mixed racial composition.

Limitations of the current analysis include the observational nature of the study. Despite the prospective nature of the present analyses, causal inference is challenging. Whereas Bonferroni-corrected associations are highlighted herein, several nominally significant associations were also observed, which may be considered hypothesis generating. We lacked statistical power to examine specific ethnic or racial subgroups. We considered various potential confounders, but additional unmeasured confounders may account for the observed associations. Change measures are challenging to analyze as small measurement errors at baseline and follow-up produce additive error that contributes to misclassification of change. However, such misclassification would likely bias toward the null. Strengths of our study include the large cohort size, wide age range, variable ethnic and racial composition, adjustment for many covariates that were routinely and robustly assessed and longitudinal study design.

Perspectives

In our multiracial, multiethnic community-based sample spanning a broad age range, aortic stiffness measures increased over time, whereas MAP decreased. The opposite directions of change in stiffness measures and MAP suggest that functional stiffening because of an increase in distending pressure does not explain the increase in aortic stiffness over time. Our analysis of previously identified metabolic traits that exhibit cross-sectional associations with vascular function revealed associations with change in vascular function, but the proportion of variance explained by metabolic factors was relatively small. The results suggest that metabolic traits may represent potential targets for further investigation of the progression of vascular stiffening over time, but much of the vascular change remains unexplained.

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Disclosures

G.F. Mitchell is the owner of Cardiovascular Engineering, Inc, a company that develops and manufactures devices to measure vascular stiffness, and serves as a consultant to and receives grants and honoraria from Novartis, Merck, Servier, and Philips.

References

1. Ben-Shlomo Y, Spears M, Boustred C, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol*. 2014;63:636–646. doi: 10.1016/j.jacc.2013.09.063.
2. Franklin SS, Lopez VA, Wong ND, Mitchell GF, Larson MG, Vasan RS, Levy D. Single versus combined blood pressure components and risk for cardiovascular disease: the Framingham Heart Study. *Circulation*. 2009;119:243–250. doi: 10.1161/CIRCULATIONAHA.108.797936.
3. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation*. 2010;121:505–511. doi: 10.1161/CIRCULATIONAHA.109.886655.
4. Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, Hughes AD, Thurston H, O'Rourke M; CAFE Investigators; Anglo-Scandinavian Cardiac Outcomes Trial Investigators; CAFE Steering Committee and Writing Committee. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation*. 2006;113:1213–1225. doi: 10.1161/CIRCULATIONAHA.105.595496.
5. Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, Benjamin EJ, Vasan RS, Mitchell GF. Aortic stiffness, blood pressure progression, and incident hypertension. *JAMA*. 2012;308:875–881. doi: 10.1001/2012.jama.10503.
6. Mitchell GF, Guo CY, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vasan RS, Levy D. Cross-sectional correlates of increased aortic stiffness in the community: the Framingham Heart Study. *Circulation*. 2007;115:2628–2636. doi: 10.1161/CIRCULATIONAHA.106.667733.
7. Mitchell GF, Wang N, Palmisano JN, Larson MG, Hamburg NM, Vita JA, Levy D, Benjamin EJ, Vasan RS. Hemodynamic correlates of blood pressure across the adult age spectrum: noninvasive evaluation in the Framingham Heart Study. *Circulation*. 2010;122:1379–1386. doi: 10.1161/CIRCULATIONAHA.109.914507.
8. Hopstock LA, Bønaa KH, Eggen AE, Grimsgaard S, Jacobsen BK, Løchen ML, Mathiesen EB, Njølstad I, Wilsgaard T. Longitudinal and secular trends in blood pressure among women and men in birth cohorts born between 1905 and 1977: the Tromsø Study 1979 to 2008. *Hypertension*. 2015;66:496–501. doi: 10.1161/HYPERTENSIONAHA.115.05925.
9. Zachariah JP, Graham DA, de Ferranti SD, Vasan RS, Newburger JW, Mitchell GF. Temporal trends in pulse pressure and mean arterial pressure during the rise of pediatric obesity in US children. *J Am Heart Assoc*. 2014;3:e000725. doi: 10.1161/JAHA.113.000725.
10. Danaei G, Finucane MM, Lin JK, Singh GM, Paciorek CJ, Cowan MJ, Farzadfar F, Stevens GA, Lim SS, Riley LM, Ezzati M; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Blood Pressure). National, regional, and global trends in systolic blood pressure since 1980: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5·4 million participants. *Lancet*. 2011;377:568–577. doi: 10.1016/S0140-6736(10)62036-3.
11. Yip JL, Khawaja AP, Chan MP, Broadway DC, Peto T, Tufail A, Luben R, Hayat S, Bhaniani A, Wareham NJ, Khaw KT, Foster PJ. Cross sectional and longitudinal associations between cardiovascular risk factors and age related macular degeneration in the EPIC-Norfolk Eye Study. *PLoS One*. 2015;10:e0132565. doi: 10.1371/journal.pone.0132565.

12. Dawber TR, Meadors GF, Moore FE Jr. Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health Nations Health*. 1951;41:279–281.
13. Splansky GL, Corey D, Yang Q, Atwood LD, Cupples LA, Benjamin EJ, D'Agostino RB Sr, Fox CS, Larson MG, Murabito JM, O'Donnell CJ, Vasan RS, Wolf PA, Levy D. The Third Generation Cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination. *Am J Epidemiol*. 2007;165:1328–1335. doi: 10.1093/aje/kwm021.
14. Liang KY, Zeger SL. Regression analysis for correlated data. *Annu Rev Public Health*. 1993;14:43–68. doi: 10.1146/annurev.pu.14.050193.000355.
15. Birru MS, Matthews KA, Thurston RC, Brooks MM, Ibrahim S, Barinas-Mitchell E, Janssen I, Sutton-Tyrrell K; SWAN Heart Study. African-American ethnicity and cardiovascular risk factors are related to aortic pulse-wave velocity progression. *Am J Hypertens*. 2011;24:809–815. doi: 10.1038/ajh.2011.57.
16. Wildman RP, Farhat GN, Patel AS, Mackey RH, Brockwell S, Thompson T, Sutton-Tyrrell K. Weight change is associated with change in arterial stiffness among healthy young adults. *Hypertension*. 2005;45:187–192. doi: 10.1161/01.HYP.0000152200.10578.5d.
17. Wildman RP, Mackey RH, Bostom A, Thompson T, Sutton-Tyrrell K. Measures of obesity are associated with vascular stiffness in young and older adults. *Hypertension*. 2003;42:468–473. doi: 10.1161/01.HYP.0000090360.78539.CD.
18. AlGhatrif M, Strait JB, Morrell CH, Canepa M, Wright J, Elango P, Scuteri A, Najjar SS, Ferrucci L, Lakatta EG. Longitudinal trajectories of arterial stiffness and the role of blood pressure: the Baltimore Longitudinal Study of Aging. *Hypertension*. 2013;62:934–941. doi: 10.1161/HYPERTENSIONAHA.113.01445.
19. El Khoudary SR, Barinas-Mitchell E, White J, Sutton-Tyrrell K, Kuller LH, Curb JD, Shin C, Ueshima H, Masaki K, Evans RW, Miura K, Edmundowicz D, Sekikawa A; ERA JUMP Study Group. Adiponectin, systolic blood pressure, and alcohol consumption are associated with more aortic stiffness progression among apparently healthy men. *Atherosclerosis*. 2012;225:475–480. doi: 10.1016/j.atherosclerosis.2012.09.015.
20. Brunner EJ, Shipley MJ, Ahmadi-Abhari S, Tabak AG, McEniery CM, Wilkinson IB, Marmot MG, Singh-Manoux A, Kivimaki M. Adiposity, obesity, and arterial aging: longitudinal study of aortic stiffness in the Whitehall II cohort. *Hypertension*. 2015;66:294–300. doi: 10.1161/HYPERTENSIONAHA.115.05494.
21. Johansen NB, Vistisen D, Brunner EJ, Tabák AG, Shipley MJ, Wilkinson IB, McEniery CM, Roden M, Herder C, Kivimäki M, Witte DR. Determinants of aortic stiffness: 16-year follow-up of the Whitehall II study. *PLoS One*. 2012;7:e37165. doi: 10.1371/journal.pone.0037165.
22. Aggoun Y, Farpour-Lambert NJ, Marchand LM, Golay E, Maggio AB, Beghetti M. Impaired endothelial and smooth muscle functions and arterial stiffness appear before puberty in obese children and are associated with elevated ambulatory blood pressure. *Eur Heart J*. 2008;29:792–799. doi: 10.1093/eurheartj/ehm633.
23. Aggoun Y, Szezepanski I, Bonnet D. Noninvasive assessment of arterial stiffness and risk of atherosclerotic events in children. *Pediatr Res*. 2005;58:173–178. doi: 10.1203/01.PDR.0000170900.35571.CB.
24. Alexander JK, Peterson KL. Cardiovascular effects of weight reduction. *Circulation*. 1972;45:310–318.
25. Lee JW, Lee DC, Im JA, Shim JY, Kim SM, Lee HR. Insulin resistance is associated with arterial stiffness independent of obesity in male adolescents. *Hypertens Res*. 2007;30:5–11. doi: 10.1291/hypres.30.5.
26. Windham BG, Griswold ME, Farasat SM, Ling SM, Carlson O, Egan JM, Ferrucci L, Najjar SS. Influence of leptin, adiponectin, and resistin on the association between abdominal adiposity and arterial stiffness. *Am J Hypertens*. 2010;23:501–507. doi: 10.1038/ajh.2010.8.
27. Kim DH, Kim C, Ding EL, Townsend MK, Lipsitz LA. Adiponectin levels and the risk of hypertension: a systematic review and meta-analysis. *Hypertension*. 2013;62:27–32. doi: 10.1161/HYPERTENSIONAHA.113.01453.
28. Sakuragi S, Abhayaratna K, Gravenmaker KJ, O'Reilly C, Srikusalanukul W, Budge MM, Telford RD, Abhayaratna WP. Influence of adiposity and physical activity on arterial stiffness in healthy children: the lifestyle of our kids study. *Hypertension*. 2009;53:611–616. doi: 10.1161/HYPERTENSIONAHA.108.123364.
29. Sutton-Tyrrell K, Newman A, Simonsick EM, Havlik R, Pahor M, Lakatta E, Spurgeon H, Vaitkevicius P. Aortic stiffness is associated with visceral adiposity in older adults enrolled in the study of health, aging, and body composition. *Hypertension*. 2001;38:429–433.
30. Zebekakis PE, Nawrot T, Thijs L, Balkestein EJ, van der Heijden-Spek J, Van Bortel LM, Struijker-Boudier HA, Safar ME, Staessen JA. Obesity is associated with increased arterial stiffness from adolescence until old age. *J Hypertens*. 2005;23:1839–1846.
31. Lakatta EG, Wang M, Najjar SS. Arterial aging and subclinical arterial disease are fundamentally intertwined at macroscopic and molecular levels. *Med Clin North Am*. 2009;93:583–604, Table of Contents. doi: 10.1016/j.mcna.2009.02.008.
32. Nichols WW, McDonald DA, O'Rourke MF. *Mcdonald's Blood Flow in Arteries Theoretical, Experimental, and Clinical Principles*. London, UK: Hodder Arnold; 2005.
33. O'Rourke MF, Safar ME, Nichols WW. Proximal aortic diameter and aortic pressure-flow relationship in systolic hypertension. *Circulation*. 2004;109:e227–e228; author reply e227. doi: 10.1161/01.CIR.0000128539.55559.3D.
34. O'Rourke MF, Yaginuma T, Avolio AP. Physiological and pathophysiological implications of ventricular/vascular coupling. *Ann Biomed Eng*. 1984;12:119–134.
35. Mukhopadhyay S, Mukherjee TK. Bridging advanced glycation end product, receptor for advanced glycation end product and nitric oxide with hormonal replacement/estrogen therapy in healthy versus diabetic postmenopausal women: a perspective. *Biochim Biophys Acta*. 2005;1745:145–155. doi: 10.1016/j.bbamcr.2005.03.010.
36. Steinberg HO, Paradisi G, Cronin J, Crowde K, Hempfling A, Hook G, Baron AD. Type II diabetes abrogates sex differences in endothelial function in premenopausal women. *Circulation*. 2000;101:2040–2046.
37. Cignarella A, Bolego C, Pinna C, Zanardo R, Eberini I, Puglisi L. The influence of sex hormones on vascular responses in the aorta of streptozotocin-diabetic male rats. *Naunyn Schmiedebergs Arch Pharmacol*. 2000;361:514–520.
38. Haitoglou CS, Tsilibary EC, Brownlee M, Charonis AS. Altered cellular interactions between endothelial cells and nonenzymatically glucosylated laminin/type IV collagen. *J Biol Chem*. 1992;267:12404–12407.
39. Tanaka S, Avigad G, Brodsky B, Eikenberry EF. Glycation induces expansion of the molecular packing of collagen. *J Mol Biol*. 1988;203:495–505.

Novelty and Significance

What Is New?

- Aortic stiffness increased over time, whereas mean arterial pressure decreased.
- Baseline and change in metabolic traits were associated with change in carotid-femoral pulse wave velocity, mean arterial pressure, forward pressure wave amplitude, pulse pressure, and characteristic impedance.
- Change in metabolic traits, rather than baseline values, explained a larger proportion of variance of change in carotid-femoral pulse wave velocity and mean arterial pressure.

What Is Relevant?

- Aortic stiffness predicts incident hypertension.
- Worsening metabolic traits may contribute to worsening vascular function and in turn incident hypertension.

Summary

Aortic stiffening was not attributable to an increase in arterial distending pressure. Associations of change in metabolic traits with change in carotid-femoral pulse wave velocity and mean arterial pressure suggest that vascular outcomes may be modifiable.

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SUPPLEMENTAL TABLE S1: Regression Model Associations Between Baseline and Change in Each Metabolic Variable Separately with Change in Each Hemodynamic Outcome

Metabolic Variables		Hemodynamic outcome variable				
Name	**Timing**	**niCFPWV (ms/m)**	**FPW (mm Hg)**	**Zc (dyne x sec/cm^5)**	**CPP (mm Hg)**	**MAP (mm Hg)**
BMI (kg/m^2)	Baseline	0.000 ± 0.013 (0.98)	-0.045 ± 0.012 (0.0002)*	-0.110 ± 0.013 (<0.0001)*	-0.062 ± 0.012 (<0.0001)*	0.062 ± 0.012 (<0.0001)*
	Change	0.065 ± 0.012 (<0.0001)*	-0.008 ± 0.011 (0.48)	-0.006 ± 0.012 (0.64)	-0.028 ± 0.011 (0.01)	0.155 ± 0.012 (<0.0001)*
Glucose (mg/dL)	Baseline	0.081 ± 0.018 (<0.0001)*	0.063 ± 0.018 (0.0003)*	0.039 ± 0.019 (0.04)	0.039 ± 0.017 (0.02)	0.082 ± 0.018 (<0.0001)*
	Change	0.091 ± 0.014 (<0.0001)*	0.019 ± 0.013 (0.15)	0.022 ± 0.014 (0.12)	0.0004 ± 0.013 (0.97)	0.063 ± 0.014 (<0.0001)*
Total:HDL-C ratio (unitless)	Baseline	0.055 ± 0.014 (0.0001)*	0.039 ± 0.014 (0.005)	0.031 ± 0.015 (0.04)	0.032 ± 0.013 (0.02)	0.069 ± 0.015 (<0.0001)*
	Change	0.065 ± 0.013 (<0.0001)*	0.023 ± 0.013 (0.06)	0.031 ± 0.014 (0.02)	0.004± 0.012 (0.73)	0.079 ± 0.013 (<0.0001)*
Triglycerides (mg/dL)	Baseline	0.087 ± 0.014 (<0.0001)*	0.050 ± 0.013 (0.0002)*	0.031± 0.014 (0.03)	0.040 ± 0.013 (0.002)	0.099 ± 0.014 (<0.0001)*
	Change	0.084 ± 0.013 (<0.0001)*	0.014 ± 0.012 (0.27)	0.012 ± 0.014 (0.36)	-0.003 ± 0.012 (0.80)	0.134 ± 0.013 (<0.0001)*
MAP (mm Hg)	Baseline	0.283 ± 0.016 (<0.0001)*	0.293 ± 0.016 (<0.0001)*	0.183 ± 0.016 (<0.0001)*	0.373 ± 0.016 (<0.0001)*	NA
	Change	0.456 ± 0.013 (<0.0001)*	0.402 ± 0.013 (<0.0001)*	0.290 ± 0.014 (<0.0001)*	0.509 ± 0.012 (<0.0001)*	NA

Results are given as the standardized regression parameter estimate (standard deviation change in dependent outcome per standard deviation difference at baseline or change in cardiometabolic trait independent variable) with standard error and p value

(in parentheses) for baseline and change pairs evaluated separately for each cardiometabolic trait. Due to skewed distribution, triglycerides were natural logarithm transformed. Data are from multivariable adjusted linear regression models with dependent variables defined as change in hemodynamic variable from baseline to follow-up exam. Covariates include baseline value for the corresponding change variable, age, age squared, sex, cohort, time between exams, baseline height, heart rate, hypertension therapy, lipid therapy, prevalent CVD, smoking, prevalent diabetes, and in the non-MAP models, additional adjustment for MAP at baseline and change in MAP.

Abbreviations- MAP, mean arterial pressure; CFPWV, carotid femoral pulse wave velocity; FPW, forward pulse wave; Zc, characteristic impedance; CPP, central pulse pressure; ln; natural logarithm transformed.

*Indicates results significant at a Bonferroni corrected p value threshold equal to 0.05 divided by 48 tests which is 0.001.

SUPPLEMENTAL FIGURE S1