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Traditional Cardiovascular Risk Factors in Relation to Left Ventricular Mass, Volume, and Systolic Function by Cardiac Magnetic Resonance Imaging

The Multiethnic Study of Atherosclerosis

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OBJECTIVES The goal of this study was to examine the cross-sectional associations of cardiovascular risk factors with left ventricular (LV) geometry and systolic function measured by cardiac magnetic resonance imaging (MRI) in the Multiethnic Study of Atherosclerosis (MESA).

BACKGROUND Cardiovascular risk factors including hypertension, smoking, and obesity are known to be associated with increased LV mass, but less is known about the association of risk factors with LV systolic function, particularly in populations without clinical cardiovascular disease.

METHODS Participants were from 4 racial/ethnic groups and were free of clinical cardiovascular disease. Blood pressure, health habits, body mass index, lipid levels, and glucose abnormalities were assessed and MRI exams performed at baseline (n = 4,869). Multivariable linear regression was used to model the association of risk factors with LV mass, end-diastolic volume, stroke volume, ejection fraction, and cardiac output.

RESULTS The mean age was 62 years, and 52% of the participants were women. After adjustment for sociodemographic variables and height, higher systolic blood pressure and body mass index were associated with larger LV mass and volumes. Current smoking and diabetes were associated with greater LV mass (+7.7 g, 95% confidence interval [CI] +5.5 to +9.9 and +3.5 g, 95% CI +1.2 to +5.8, respectively), and with lower stroke volume (−1.9 ml, 95% CI −3.3 to −0.5 and −4.5 ml, 95% CI −6.0 to −3.0, respectively) and lower ejection fraction (−1.6%, 95% CI −2.1 to −1.0 and −0.8%, 95% CI −1.5 to −0.2, respectively).

CONCLUSIONS In this cohort free of clinical cardiovascular disease, modifiable risk factors were associated with subclinical alterations in LV size and systolic function as detected by cardiac MRI. (J Am Coll Cardiol 2006;48:2285–92) © 2006 by the American College of Cardiology Foundation

Large epidemiologic studies of left ventricular (LV) geometry and systolic function have generally relied upon echocardiography (1–3). High systolic blood pressure, smoking, and obesity have been consistently associated with elevated LV mass, but less information is available about the association of traditional cardiovascular risk factors with LV systolic function, particularly in asymptomatic populations. Magnetic resonance imaging (MRI) of the heart provides accurate and reproducible measurement of LV mass, volumes, and systolic function (4), is not limited by acoustic windows as is echocardiography, does not rely on geometric assumptions about the shape of the ventricle, and does not require exposure to ionizing radiation. Thus, MRI is an appropriate noninvasive technology for investigating subclinical alterations in LV size and systolic function.

The Multiethnic Study of Atherosclerosis (MESA) is the first large-scale application of cardiac MRI in a multicenter study and in a multiethnic population. Most previous studies of cardiac MRI have been limited by the inclusion of small numbers of participants, a focus on patients with pre-existing cardiovascular disease, or incomplete information on risk factors. We used data from the baseline examination in the MESA to examine the cross-sectional relationships of traditional cardiovascular risk factors with 5 MRI measurements—LV mass, end-diastolic volume, stroke volume, ejection fraction, and cardiac output—in people without clinical cardiovascular disease.

METHODS

Setting. The MESA was designed to investigate the pathogenesis of atherosclerosis in 4 racial/ethnic groups by providing accurate measurement of early cardiovascular disease and its progression. Between July 2000 and September 2002, 6,814 men and women aged 45 to 84 years were

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Abbreviations and Acronyms

CARDIA	= Coronary Artery Risk Development in Young Adults
HDL	= high-density lipoprotein
ICC	= intraclass correlation coefficient
LDL	= low-density lipoprotein
LV	= left ventricular
MESA	= Multiethnic Study of Atherosclerosis
MRI	= magnetic resonance imaging

enrolled from 6 U.S. communities (5,6). Potential participants were contacted by random digit dialing or by informational brochures mailed to households identified by sampling frames such as census data or by geographic criteria. Institutional review boards at all study centers approved the study protocol, and informed consent was obtained from every participant. Participants were recruited from 4 ethnic groups: white, African American, Hispanic, and Asian (of Chinese descent); race and ethnicity were self-reported. All participants were free of clinically recognized cardiovascular disease at enrollment.

Baseline examination. Participants underwent an extensive baseline evaluation, including measurement of height, weight, and waist circumference, and assessment by questionnaire of smoking, alcohol intake, educational attainment, exercise (including team sports, dance, moderate individual activities or conditioning, vigorous dual sports or conditioning, and walking for exercise), current medications, and physician diagnoses of hypertension and diabetes (5). Blood pressure was measured 3 times in the seated position with a Dinamap device (Critikon, Tampa, Florida) (7); the mean of the second and third measurements was used in the analysis. Heart rate was monitored and recorded at the time of the MRI exam. Glucose, triglycerides, and total and high-density lipoprotein (HDL) cholesterol levels were measured after a 12-h fast, and low-density lipoprotein (LDL) cholesterol level was calculated with the Friedewald equation (8).

Magnetic resonance imaging. Consenting participants underwent a cardiac MRI scan a median of 16 days after the baseline evaluation; 95% were completed by 11 weeks after the baseline examination. Participation in the MRI exam was voluntary. The MRI exams were performed using scanners with 1.5-T magnets as previously described (9). All imaging was performed with a 4-element phased-array surface coil positioned anteriorly and posteriorly, electrocardiographic gating, and brachial artery blood pressure monitoring. Imaging consisted of fast gradient echo cine images of the left ventricle with time resolution <50 ms. Functional parameters and mass were determined by volumetric imaging. Imaging data were read using MASS software (version 4.2, Medis, Leiden, the Netherlands) at a single reading center by readers trained in the MESA protocol and without knowledge of risk factor information. Papillary muscles were included in the LV volumes and excluded from LV mass. Cardiac output was calculated as stroke volume (end-diastolic volume − end-systolic volume) × heart rate. Ejection fraction was calculated as stroke volume/end-diastolic volume. The reliability of the MRI readings was determined by calculating for a set of 155 duplicate readings the intraclass correlation (ICC) as the ratio of the variance of the variable if precisely meaured (without measurement error) over the observed variance of the variable (with measurement error). An ICC reliability estimate of 0.95 means that 5% of the total variability is attributed to reader measurement error. For LV mass, ICC was 0.97 (95% confidence interval [CI] 0.96 to 0.98), for end-diastolic volume 0.98 (95% CI 0.97 to 0.99), and for end-systolic volume 0.95 (95% CI 0.93 to 0.96).

Statistical analysis. We identified key variables that assess traditional cardiovascular risk factors: systolic blood pressure, diastolic blood pressure, tobacco use, alcohol use, exercise (expressed as total MET-hours/week, where MET is defined as the ratio of work metabolic rate to a standard resting metabolic rate [10]), body mass index, LDL and HDL cholesterol, and glucose abnormalities. Participants were classified into 3 mutually exclusive categories regarding glucose metabolism: those with a fasting glucose ≥126 mg/dl or who used insulin or hypoglycemic agents were classified as having diabetes; nondiabetics with fasting glucose ≥100 and <126 mg/dl were classified as having impaired fasting glucose; and nondiabetics with fasting glucose <100 mg/dl were classified as normoglycemic (11). Risk factor data were missing for <0.5% of participants for all variables except alcohol use and LDL cholesterol, which were missing for <1.5% of participants.

We examined plots of the mean value of each MRI measurement with levels of each risk factor after adjustment for the sociodemographic characteristics of age, gender, race, and clinic location and adjustment for height as a measure of body size. Linear relationships with all MRI measurements were apparent for age, alcoholic drinks/week, body mass index, LDL and HDL cholesterol, and MET-hours/week of exercise. For systolic and diastolic blood pressure, we explored the possibility of nonlinear associations by including squared terms in the regression models. Among the tobacco use categories, only current cigarette smoking was associated with the MRI measurements, and therefore current smoking was modeled as a dichotomous variable.

We used multivariable linear regression to identify traditional cardiovascular risk factors independently associated with the cardiac MRI measurements; significance was declared at $p < 0.05$. All of the risk factors were retained in the models in addition to the sociodemographic variables and height. In a series of models, we introduced interaction terms between each significant cardiovascular risk factor and the sociodemographic variables of age (<65 or ≥65 years), gender, and race; significance for interactions was declared at $p < 0.002$ after Bonferroni correction for an average of 21 subgroup comparisons per MRI measurement. In sensitivity analyses, height squared (12) and height to the 2.7th power (13) were examined as alternatives to height as methods of adjustment for body size. Body surface area was not used to adjust for body size because obesity was of interest as a traditional cardiovascular risk factor and adjustment for body surface area attenuates associations between obesity and LV mass. Waist circumference at the baseline exam and self-reported body mass index at ages 20 and 40 years were examined as alternatives to baseline body mass index as measures of obesity. The association of systolic and diastolic blood pressures with ejection fraction was examined across prespecified categories of blood pressure (14). All analyses were conducted using Stata Statistical Software release 8.0 (Stata Corp., College Station, Texas). The analyses were based on the updated MESA database, which incorporated minor corrections through November 2005.

RESULTS

Of the 6,814 MESA participants, 5,004 (73%) completed the cardiac MRI and had technically adequate data. Reasons for not completing the cardiac MRI included ineligibility (7% out of 6,814), usually because of metallic fragment, implant, or device, inability (14%), usually because of claustrophobia, refusal (3%), mechanical problem with the scanner (0.4%), or unknown (1%). Data on 1 or more cardiovascular risk factors were missing for 135 participants (3%), and they were excluded. Compared with those not included in the analysis (n = 1,945), the 4,869 participants included were on average slightly younger (62 vs. 64 years) and had lower average systolic blood pressure (125 vs. 130 mm Hg) and body mass index (27.7 vs. 29.8 kg/m^2); a smaller proportion were African American (26% vs. 33%) and a larger proportion Asian (13% vs. 9%), and a smaller proportion had treated hypertension (31% vs. 38%) or diabetes (13% vs. 18%) (all differences significant at $p < 0.05$). Among those included in the analysis, the mean age was 62 years (SD = 10), 52% were women, 39% white, 26% African American, 22% Hispanic, and 13% Asian (Table 1). Considering men and women together, 31% had treated hypertension, 27% had impaired fasting glucose, and 13% had diabetes. Only 13% were current smokers, and the mean number of alcoholic drinks/week was 1.9 in women and 6.3 in men.

Data were available for all 4,869 participants for all 5 MRI measurements of interest except cardiac output, which was available for 4,850 participants. The gender-specific means and standard deviations of the MRI measurements are shown in Table 2. For LV mass, the mean (SD) expressed in units of grams divided by height in meters was 77 (16) g/m in women and 97 (21) g/m in men.

The results from the 5 separate multivariable statistical models for the cardiac MRI measurements are shown in the 5 columns of Table 3. The first row of the table indicates the proportion of the variability in each MRI measurement explained by the full model (including all the cardiovascular risk factors, the sociodemographic variables, and height), i.e., the adjusted r^2. The second row indicates the proportion of the variability remaining after adjustment for sociodemographic variables and height that was explained by the cardiovascular risk factors. Below, the coefficients and 95% CI listed for each risk factor express the mean difference in each MRI measurement associated with that risk factor after

Table 1. Characteristics of 4,869 MESA Participants With Cardiac MRI Included in the Analysis

	Women (n = 2,546)	Men (n = 2,323)
Age, yrs	61 (10)	62 (10)
Race, %		
White	39.2	38.9
African American	26.8	24.6
Hispanic	21.1	23.2
Asian	12.9	13.3
High school graduate or less, %	37.8	30.3
Systolic BP, mm Hg	126 (23)	125 (19)
Diastolic BP, mm Hg	69 (10)	75 (9)
Hypertension,* %	43.3	40.6
Treated hypertension,† %	32.8	28.8
Current cigarette smoker, %	11.0	14.5
Alcohol use, drinks/week	1.9 (5.1)	6.3 (10.8)
Exercise, MET-h/wk	23.4 (33.8)	30.2 (44.3)
Body mass index, kg/m^2	28.0 (5.6)	27.4 (4.1)
LDL cholesterol, mmol/l (mg/dl)	3.0 (0.8) [117 (32)]	3.0 (0.8) [117 (31)]
HDL cholesterol, mmol/l (mg/dl)	1.5 (0.4) [57 (15)]	1.2 (0.3) [45 (12)]
Use of lipid-lowering medication, %	16.4	14.6
Impaired fasting glucose, %	22.2	31.6
Diabetes, %	11.4	14.0

Values expressed as mean ± SD or percentage. *Hypertension was defined as BP ≥140 mm Hg systolic or ≥90 mm Hg diastolic, or with treated hypertension. †Treated hypertension was defined as a history of a physician diagnosis of hypertension and taking antihypertensive medication.

BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MRI = magnetic resonance imaging.

Table 2. Gender-Specific Mean and Standard Deviation of LV Mass, End-Diastolic Volume, Stroke Volume, Ejection Fraction, and Cardiac Output by Cardiac MRI in MESA Participants

	Women (n = 2,546*)		Men (n = 2,323†)	
	Mean	SD	Mean	SD
LV mass (g)	124	27	169	37
LV end-diastolic volume (ml)	114	24	140	33
LV stroke volume (ml)	81	17	93	21
LV ejection fraction (%)	71	7	67	7
Cardiac output*† (l/min)	5.4	1.4	6.0	1.5

*n = 2,536 for cardiac output only. †n = 2,314 for cardiac output only.
LV = left ventricular; MRI = magnetic resonance imaging.

adjustment for all of the other cardiovascular risk factors in the model, the sociodemographic variables, and height. For continuous variables, such as blood pressure, the associations with MRI measurements are expressed in standard deviation units. For example, for each standard deviation (21 mm Hg) increase in systolic blood pressure, the mean LV mass was 9.6 g greater (95% CI 8.5 to 10.8). A term for the square of systolic blood pressure was included only in the models for ejection fraction and cardiac output; diastolic blood pressure squared was included only in the model for ejection fraction.

LV mass. The LV mass was directly related to systolic blood pressure, current smoking, exercise, body mass index, and diabetes after adjustment for the other variables in the model and was weakly inversely related to LDL cholesterol (Table 3). After adjustment for the sociodemographic variables and height, the proportion of the remaining variability in LV mass explained by the cardiovascular risk factors was 26.1%.

Although risk factor relationships with LV mass were generally similar across subgroups defined by age, gender, and race, the associations with elevated systolic blood pressure were more prominent in men than in women (+13.5 vs. +6.9 g per standard deviation of systolic blood pressure; $p < 0.0005$) and in participants under 65 years of age than in those 65 and older (+12.9 vs. +7.2 g per standard deviation of systolic blood pressure; $p < 0.0005$), and the association with body mass index was stronger in men than in women (+15.0 vs. +10.5 g per standard deviation of body mass index; $p < 0.0005$).

LV end-diastolic volume. The LV end-diastolic volume was directly related to systolic blood pressure, exercise, body mass index, and HDL cholesterol level and inversely related to diastolic blood pressure, LDL cholesterol level, impaired fasting glucose, and diabetes after adjustment for the other variables in the model. The proportion of the remaining variability in LV end-diastolic volume after adjustment for the sociodemographic variables and height that was explained by the cardiovascular risk factors was 12.2%. Relationships were similar across subgroups defined by age, gender, and race.

Table 3. Multivariable Analysis of Traditional Cardiovascular (CV) Risk Factors in Relation to LV Mass, Volumes, and Systolic Function

	LV Mass (g)	LV End-Diastolic Volume (ml)	LV Stroke Volume (ml)	LV Ejection Fraction (%)	Cardiac Output§ (l/min)
Proportion of variability explained by full model*	59.6%	43.8%	34.9%	17.8%	22.3%
Proportion of variability explained by the CV risk factors†	26.1%	12.2%	14.5%	2.4%	11.2%
Risk factor, coefficient‡ (95% confidence interval)					
Systolic BP, per 21 mm Hg	9.6 (8.5, 10.8)¶	6.4 (5.3, 7.5)¶	5.5 (4.8, 6.2)¶	1.2 (0.9, 1.5)¶	0.26 (0.20, 0.33)¶
Systolic BP, squared, per 21 mm Hg^2				−0.1 (−0.3, 0.0)	−0.04 (−0.07, −0.02)¶
Diastolic BP, per 10 mm Hg	−1.1 (−2.2, 0.0)	−4.3 (−5.3, −3.3)¶	−4.3 (−5.0, −3.6)¶	−1.1 (−1.4, −0.8)¶	−0.05 (−0.11, 0.01)
Diastolic BP squared, per 10 mm Hg^2				−0.3 (−0.4, −0.1)¶	
Current smoking	7.7 (5.5, 9.9)¶	0.9 (−1.2, 2.9)	−1.9 (−3.3, −0.5)¶	−1.6 (−2.1, −1.0)¶	−0.14 (−0.25, −0.03)#
Alcohol intake, per 9 drinks/week	0.4 (−0.3, 1.2)	−0.4 (−1.1, 0.3)	−0.2 (−0.7, 0.2)	0.0 (−0.2, 0.2)	−0.03 (−0.07, 0.01)
Exercise, per 27 MET-h/week	0.9 (0.4, 1.4)¶	0.7 (0.2, 1.1)¶	0.5 (0.2, 0.8)¶	0.0 (−0.1, 0.2)	0.00 (−0.03, 0.03)
Body mass index, per 5 kg/m^2	11.7 (10.9, 12.6)¶	8.4 (7.6, 9.2)¶	5.9 (5.3, 6.4)¶	0.0 (−0.2, 0.2)	0.41 (0.37, 0.45)¶
LDL cholesterol, per 31 mg/dl	−1.1 (−1.8, −0.4)¶	−0.9 (−1.6, −0.2)#	−0.6 (−1.1, −0.2)¶	0.0 (−0.2, 0.2)	−0.04 (−0.08, 0.00)#
HDL cholesterol, per 15 mg/dl	0.1 (−0.7, 1.0)	1.8 (1.0, 2.6)¶	1.1 (0.6, 1.7)¶	0.0 (−0.3, 0.2)	0.07 (0.03, 0.11)¶
Impaired fasting glucose (vs. normoglycemic)	−1.2 (−2.9, 0.5)	−3.8 (−5.5, −2.2)¶	−2.5 (−3.6, −1.4)¶	0.2 (−0.3, 0.6)	0.02 (−0.07, 0.11)
Diabetes (vs. normoglycemic)	3.5 (1.2, 5.8)¶	−4.6 (−6.8, −2.4)¶	−4.5 (−6.0, −3.0)¶	−0.8 (−1.5, −0.2)¶	0.12 (0.00, 0.24)

*Proportion of the total variability (adjusted r^2) explained by the sociodemographic variables, height, and the cardiovascular risk factors. †Proportion of the variability remaining after adjustment for sociodemographic variables and height that was explained by the cardiovascular risk factors. ‡Adjusted for sociodemographic variables (age, gender, race/ethnicity, clinic site), height, and the risk factors listed in the leftmost column; systolic BP squared was included only in the models for ejection fraction and cardiac output; diastolic blood pressure squared was included only in the model for ejection fraction. §Data were available on cardiac output for 4,850 participants; for all other MRI measurements, data were available for 4,869 participants. ¶Test for significance of coefficient: $p < 0.01$. #Test for significance of coefficient: $p < 0.05$.
BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LV = left ventricular.

LV stroke volume. The associations of risk factors with LV stroke volume were similar to those for end-diastolic volume. Like end-diastolic volume, after adjustment for the other variables in the model, stroke volume was directly related to systolic blood pressure, exercise, body mass index, and HDL cholesterol and inversely related to diastolic blood pressure, LDL cholesterol, impaired fasting glucose, and diabetes. In addition, stroke volume was inversely related to current smoking. After adjustment for the sociodemographic variables and height, the proportion of variability in LV stroke volume explained by the cardiovascular risk factors was 14.5%.

Associations were similar in subgroups defined by gender and race, but the inverse association with diastolic blood pressure was more prominent in participants 65 and older than in those under 65 years of age (−5.1 vs. −3.7 ml per standard deviation of diastolic blood pressure; $p = 0.001$).

LV ejection fraction. Ejection fraction was directly related to systolic blood pressure and inversely related to diastolic blood pressure, current smoking, and diabetes, after adjustment for the other variables in the model. The coefficients for the square of systolic and the square of diastolic blood pressure were negative. These findings suggest that ejection fraction was directly related to systolic blood pressure except at the highest levels of systolic blood pressure, where an inverse relationship was seen, and that ejection fraction was inversely related to diastolic blood pressure throughout the range of values, especially at the highest levels of diastolic blood pressure. The results from these models were consistent with plots of mean ejection fraction by categories of systolic (Fig. 1A) and diastolic blood pressure (Fig. 1B) adjusted for all of the other variables in the multivariable model. Only 2.4% of the remaining variability in ejection fraction was explained by the cardiovascular risk factors considered after adjustment for the sociodemographic variables and height (Table 3).

Risk factor relationships with ejection fraction were similar in age, gender, and race subgroups. The relationships of ejection fraction with systolic and diastolic blood pressure levels were similar in users and nonusers of antihypertensive medications, but mean ejection fraction was higher at any given level of systolic or diastolic blood pressure in those with medically treated hypertension than in those with untreated hypertension.

Cardiac output. Cardiac output was directly related to systolic blood pressure, body mass index, and HDL cholesterol and inversely related to the square of systolic blood pressure, current smoking, and LDL cholesterol after adjustment for the other variables in the model. For systolic blood pressure, these results suggest a positive relationship at most levels of systolic blood pressure, but lower mean cardiac output at the highest levels. After adjustment for the sociodemographic variables and height, the proportion of the remaining variability in cardiac output explained by the cardiovascular risk factors was 11.2%. Relationships were similar across gender and race subgroups; the positive linear association with systolic blood pressure was stronger in participants under 65 than in those 65 years and older (+0.29 vs. +0.21 l/min per standard deviation of systolic blood pressure; $p = 0.001$).

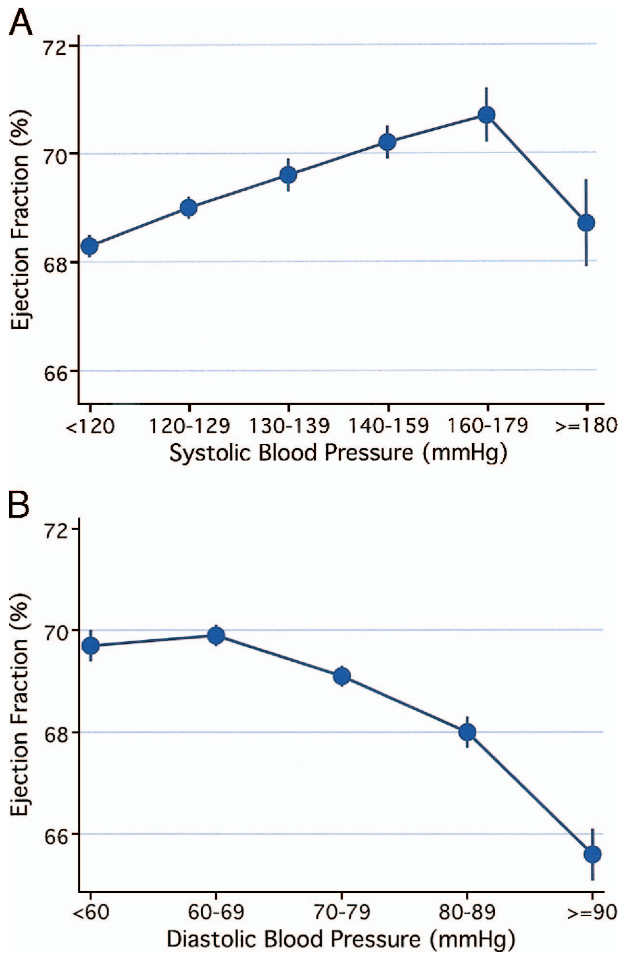

Figure 1. Adjusted mean ejection fraction (with standard error) for various levels of systolic **(A)** and diastolic **(B)** blood pressure.

The inclusion of serum creatinine or educational status in the models did not materially change the coefficients for the risk factors listed in Table 3. In models where adjustment for height was replaced with adjustment for height squared or height to the 2.7th power, the coefficients associated with the cardiovascular risk factors were virtually identical to those presented in Table 3. In models where systolic and diastolic blood pressure were replaced with pulse pressure, pulse pressure was strongly and positively associated with all of the MRI measurements. For all MRI measurements, relationships with current body mass index were similar to relationships with body mass index at age 40 years and slightly stronger than relationships with body mass index at age 20 years. The relationship of waist measurement with the MRI measurements was similar to that of body mass index. The associations of LDL cholesterol levels with the MRI measurements studied were slightly but not significantly weaker in users than in nonusers of lipid-lowering agents. Among diabetics, the duration of use of diabetes medication was positively related to LV mass, but not to the other measurements. Among ever smokers, pack-years of cigarette smoking was inversely related to end-diastolic volume and stroke volume after adjustment for current smoking. Among participants with hypertension, the associations of cardiovascular risk factors with each of the MRI measurements were similar in those taking and those not taking antihypertensive medications.

DISCUSSION

In this cohort free of clinical cardiovascular disease, modifiable cardiovascular risk factors were associated with subclinical alterations in LV mass, volumes, and systolic function as determined by cardiac MRI. After adjustment for sociodemographic variables and height, higher systolic blood pressure and body mass index were associated, as expected, with higher LV mass and larger volumes. In the normotensive range and up through systolic blood pressures of 179 mm Hg, ejection fraction was directly related to systolic blood pressure, but at systolic blood pressures of ≥180 mm Hg, an inverse relationship was observed. By contrast, the higher the diastolic blood pressure, the lower the ejection fraction, with a particularly low average ejection fraction at the highest levels of diastolic blood pressure. Current smoking and diabetes were associated with higher LV mass but lower stroke volume and ejection fraction, and high HDL cholesterol was associated with higher stroke volume and cardiac output. Some associations with cardiovascular risk factors were more prominent in men than in women and differed in older compared with younger participants, but associations of risk factors with MRI measurements did not differ significantly across racial/ethnic groups.

The accuracy and reproducibility of cardiac MRI permitted us to identify relationships of cardiovascular risk factors with subclinical alterations in LV size and systolic function that have been difficult to detect using previously available noninvasive methods. The reproducibility of the MRI measurements compared favorably with other large population studies that used echocardiography. For example, in the CARDIA (Coronary Artery Risk Development in Young Adults) study, the technical error of measurement for reading LV mass ranged from 8% to 14% (1), and in MESA, as calculated from the same 155 duplicate readings described in the Methods section, it was 6.17% (95% CI 5.29 to 7.04). The large sample size in this study allowed the detection of very small differences in mass, volumes, and systolic function in relation to risk factors. These small differences may be of little clinical significance to the individual. However, if these differences persist and accumulate over time, they could lead to clinically important alterations in LV size or systolic function, and on a population level such changes may assume public health importance. In addition, the accuracy of this method makes it suitable to follow the effects of treatments such as blood pressure-lowering medications in individuals over time.

Strengths of this study include the representation of several ethnic groups and both genders, a wide age range, a broad range of levels of most cardiovascular risk factors, and recruitment from 6 geographically distinct areas of the U.S. Extensive information on cardiovascular risk factors was available, and the reliability of the MRI readings was excellent. Nonetheless, there was a limited range of levels of certain cardiovascular risk factors, including alcohol intake and exercise, limiting our ability to assess their relationships with cardiac size and function. The MRI exams were not done on 27% of the participants, and those with an MRI exam had on average fewer cardiovascular risk factors than those without an exam. The MESA cohort includes only people without clinically manifest cardiovascular disease; the associations described here may differ from those in populations with clinically evident disease. Finally, because we had only a single cardiac MRI examination, we were not able to examine the longitudinal association of risk factors with change in LV geometry and systolic function.

The strong positive association of body mass index with LV mass and volumes was expected and may reflect both the larger ventricular size required for greater lean body mass and a component related to adiposity. We were not able to measure lean body mass and fat mass accurately with the measurements of body size available in this study and therefore were not able to determine the extent to which the higher LV mass, volumes, and cardiac output seen with higher body mass index are due to greater lean body mass versus excess adiposity. Indexation of each of the MRI measurements by height and weight in healthy nonobese individuals may allow better insight into the relationship of adiposity with LV geometry and function.

Our findings for risk factor associations with LV mass are in general agreement with the echocardiographic findings from the CARDIA study (1) and the Cardiovascular Health Study (2). In one or both of these studies, LV mass was directly associated with weight, systolic blood pressure, current smoking, and history of hypertension and was inversely associated with diastolic blood pressure. Similar findings by echocardiography were reported from 2 European studies of men: a study of 475 men from the general population of Uppsala County, Sweden (15), and a French study of 843 healthy men 47 to 61 years of age (16). In the French study, body mass index at age 20 years was a stronger determinant of LV mass than current body mass index, whereas in the present study current body mass index was more strongly associated with LV mass. In the Uppsala study, elevated LDL/HDL cholesterol ratio at baseline was associated with the development of LV hypertrophy 20 years later (15), whereas in MESA high LDL was associated cross-sectionally with slightly lower LV mass. Unlike the present analysis, the Uppsala study did not consider the joint contributions of a variety of cardiovascular risk factors in a multivariable model; this difference in analytic methods may explain in part the apparently discrepant findings. A direct association of fasting insulin and triglyceride levels with LV hypertrophy was found in men only in an unadjusted analysis of data from normotensive participants in the Tecumseh study (17), but in a multivariable analysis including other cardiovascular risk factors neither of these associations persisted. By contrast, in multivariable analyses in MESA, diabetes was associated with greater LV mass in both men and women, and diabetes and/or glucose intolerance was associated with reduced end-diastolic volume, stroke volume, and ejection fraction.

Associations of potentially modifiable risk factors with LV mass are important because LV mass is a strong predictor of sudden cardiac death (18), cardiovascular disease (19), and all-cause mortality in both middle-aged (20) and elderly individuals (21). A graded relationship with cardiovascular morbidity and all-cause mortality throughout the range of observed values for LV mass has been demonstrated in people with hypertension (22,23), and lower LV mass during antihypertensive treatment has been associated with lower risk of cardiovascular end points independent of the extent of blood pressure-lowering (24). Furthermore, clinical trials suggest that in people with hypertension, long-term antihypertensive therapy may reduce LV mass as measured by echocardiography (25,26) and that weight loss results in reduction in LV mass (27). Whether treatment of other risk factors, such as smoking and diabetes, would result in reduction of LV mass is not clear but may become amenable to study through the use of cardiac MRI.

In contrast to LV mass, there is considerably less information on the associations of cardiovascular risk factors with LV volumes or systolic function in populations without recognized cardiovascular disease. Despite the known acute effects of nicotine to increase heart rate and contractility, stroke volume, ejection fraction, and cardiac output were on average slightly lower in the present study in current smokers than in nonsmokers. The mechanisms underlying these observations and the observed associations of high HDL cholesterol and low LDL cholesterol with higher volumes and cardiac output require further study.

In summary, in this cohort free of clinical cardiovascular disease, modifiable risk factors were associated with subclinical alterations in LV size and systolic function. The proportion of variability within all the cardiac MRI measurements explainable by traditional cardiac risk factors was small, however, and this was particularly true for ejection fraction. The high degree of reproducibility of cardiac MRI should allow the detection of subtle deterioration or improvement in LV size and function. Additional study is needed of risk factors and their treatment in relation to the new development or progression of LV dysfunction and of the relationship of subclinical alterations of cardiac size and function with outcomes such as myocardial infarction and sudden cardiac death. Longitudinal study of the MESA cohort and other cohorts may provide important information in this regard.

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