Echocardiographic evaluation of wall motion (WM) is a simple, well-validated method to assess segmental left ventricular (LV) function. The presence of qualitative WM abnormalities has been demonstrated to be an independent predictor of cardiovascular events in groups of patients with myocardial infarction (MI), unstable angina, typical chest pain, and congestive heart failure (CHF); however, regional WM abnormalities may also occur without history or clinical and ECG signs of coronary artery disease. No information exists on the association of echocardiographic WM abnormalities with subsequent cardiovascular morbidity and mortality in unselected adults without overt cardiovascular disease (CVD). Accordingly, we examined whether echocardiographic LV WM abnormalities predict cardiovascular outcomes in a population-based sample of adults without overt CVD, independently of established cardiovascular risk factors.
1989 to 1992, the study cohort included adults aged 45 to 74 years in participating communities. Extensive characterization of participants included standardized measurement of seated brachial blood pressure; measures of body habits, including body mass index and waist/hip ratio; fasting glucose, insulin, lipid, and lipoprotein concentrations; and 2-hour glucose tolerance test and glycosylated hemoglobin levels. Arterial hypertension was defined by recommendations of the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Diabetes mellitus was diagnosed by World Health Organization criteria or current use of hypoglycemic therapy. Microalbuminuria was defined as urine albumin/creatinine ≥30 and <300 mg and macroalbuminuria as albumin/creatinine ≥300 mg/g. A total of 3501 participants in the second SHS examination (between 1993 and 1995) underwent an echocardiographic examination and were considered for the present study.

Participants with prevalent coronary heart disease, stroke, or CHF at the time of echocardiographic examination were excluded from the present analysis. Prevalent coronary heart disease was diagnosed by self-report at the first SHS examination or on the basis of subsequent MI, confirmed by a physician-comprised morbidity committee (blinded to echocardiographic data), coronary angiographic documentation of major epicardial coronary artery obstruction, PTCA, coronary bypass, or major Q-wave Minnesota codes for MI, stroke, sudden death due to definite coronary heart disease, or CHF. Similarly, medical records were reviewed by an expert physician panel to identify nonfatal cardiovascular events that occurred after the second SHS examination. In patients experiencing more than 1 adverse event, only the first event was considered in analyses of the combined end point of fatal and nonfatal cardiovascular events. Follow-up for nonfatal events and mortality was 99% and 99.8% complete, respectively. Echocardiogram reports were returned to participants’ healthcare providers, but few if any evaluations for coronary artery disease were provoked in 1993 to 1995 by these reports.

### Statistical Analysis

Descriptive statistics for the various covariates are shown as either percentages or means with SDs. In the presence of skewed distributions, the median was calculated and the interquartile range (between the 25th and 75th percentiles) given. χ2 Statistics were used to identify categorical variable differences, whereas 1-factor ANOVA was used to identify continuous variable differences among groups without or with segmental or global WM abnormalities, with multiple comparisons by the REGW-F post hoc test (Ryan, Einot, Gabriel, & Welsch F test) when needed. The Kruskal-Wallis test was used to identify differences of C-reactive protein among groups because of skewed distribution.

Event rates were displayed by Kaplan-Meier plots. Log cumulative hazard functions were computed by Cox proportional hazards analysis with forced entry of covariates. Age, gender, waist-hip ratio, systolic blood pressure, and diabetes mellitus were considered together with WM abnormalities in all models. Other models were performed that additionally considered established clinical predictors of cardiovascular events (current smoking, total/HDL cholesterol, and serum creatinine), plus markers of preclinical CVD (microalbuminuria and LV mass index), and, finally, all of the above plus markers of inflammation (C-reactive protein and fibrinogen). Hazard ratios (HRs) with 95% CIs for all first cardiovascular events and for cardiovascular death were examined. For each baseline characteristic, a univariable proportional hazards regression model was used to estimate the HR and its 95% CI. Finally, likelihood functions from the Cox models with or without WM abnormalities (both adjusted for standard cardiovascular risk factors) were compared. The difference between 2 likelihood functions has a 1-degree-of-freedom χ2 distribution.

To assess the ability of Cox models with or without segmental WM abnormalities to discriminate participants who experienced cardiovascular events from those who did not, we used a version of the c statistic, which was calculated on the basis of all possible pairs of participants, at least 1 of whom had CVD. Analogous to the area under the receiver operating characteristic curve, c represents an estimate of the probability that the Cox model assigns a higher risk to participants who develop a cardiovascular event early in the follow-up period than to those who develop cardiovascular events late or never develop the disease in the follow-up period. A c value of ≥0.7 indicates good discrimination ability, and the closer the c value is to 1.0, the better is the discrimination ability. Interaction between WM abnormalities and gender, diabetes mellitus, or hypertension was tested by adding cross-product terms of WM abnormalities and these variables into the models. To place the results of the present analyses in context, univariable Kaplan-Meier curves were constructed for SHS participants excluded from the present analyses because of clinically recognized CVD versus the groups with or without segmental WM abnormalities in the present report and compared by the log-rank method. The null hypothesis was rejected at 2-tailed P<0.05. Analyses were performed with SPSS 12.0.

The authors had full access to and take full responsibility for the integrity of the data and performed all reported analyses. All authors have read and agree to the manuscript as written.
characteristics of study population in relation to WM abnormalities

A total of 2864 eligible participants (mean age 60±8 years; 1839 women [64%]) with complete baseline WM assessment and without prevalent CVD at the time of echocardiographic examination were included in the present analysis. At echocardiographic evaluation, 140 participants (5%) had segmental WM abnormalities and 42 (1.5%) had global WM abnormalities. Among participants with segmental WM abnormalities, 105 (75%) had mild hypokinesia in at least 2 contiguous segments in a coronary territory, 23 (17%) had moderate hypokinesia, and 12 (8%) had severe hypokinesia, akinesia, or dyskinesia. Similarly, among participants with global WM abnormality, hypokinesia was classified as mild in 34 participants (82%), moderate in 4 (10%), and severe in 4 (8%).

Clinical characteristics of the study population are reported in Table 1. Participants with WM abnormalities were more likely to be male; had higher mean C-reactive protein, fibrinogen, and creatinine; and were more likely to have microalbuminuria or macroalbuminuria than participants with normal WM. Progressively higher mean LV mass and lower LV ejection fraction were observed in participants with segmental and global WM abnormalities than in those with normal WM. Body mass index was lower in participants with segmental WM abnormalities than in those with normal or global WM abnormality. Participants with segmental WM abnormalities had higher systolic, diastolic, and pulse pressures and higher prevalence of diabetes mellitus than participants with normal WM. The average time from the echocardiographic examination to the first cardiovascular event or to the end of follow-up in the present study cohort was 8.2±2.2 years.

Prognostic Impact of Segmental WM Abnormalities

The cumulative incidences of combined fatal and nonfatal cardiovascular events and of cardiovascular mortality were
2.5- to 3-fold higher in participants with segmental WM abnormalities than in those with normal WM (both \( P < 0.0001 \); Table 2). Participants with segmental WM abnormalities also had higher cumulative incidences of each of the component end points.

In univariable Cox models, segmental WM abnormalities (Table 2; Figures 1 and 2) were associated with more frequent occurrence over time of both first cardiovascular events and cardiovascular death. These associations were confirmed after adjustment for age, gender, waist-hip ratio, systolic blood pressure, and diabetes mellitus (Table 2). Of note, tests of interaction were not significant between segmental WM abnormalities and gender (\( P = 0.30 \) and 0.06), diabetes mellitus (\( P = 0.87 \) and 0.09), or hypertension (\( P = 0.99 \) and 0.36) for cardiovascular events and cardiovascular mortality.

Additional analyses were performed with inclusion of additional markers of risk for CVD (current cigarette smoking, total/high-density lipoprotein cholesterol, and serum creatinine). In these models, segmental WM abnormalities remained a significant predictor of first cardiovascular event (HR 1.9, 95% CI 1.3 to 2.7, \( P = 0.001 \)) but not of cardiovascular mortality (HR 1.5, 95% CI 0.8 to 2.7, \( P > 0.20 \)). The \( c \)-statistic was 0.70 for the Cox model for first cardiovascular events with segmental WM, which indicates good discrimination ability and was modestly higher than the \( c \)-statistic of 0.69 for the model without WM abnormalities. Additionally, comparison between \( -2 \log \) likelihood values demonstrated that the likelihood of cardiovascular events was significantly higher in the model including than in the model excluding WM abnormalities (\( P < 0.0001 \)). In a further model that added microalbuminuria and LV mass index (as markers of preclinical CVD) to the previous covariates, the association of WM abnormalities with total cardiovascular events was not altered substantially (HR 2.0, 95% CI 1.4 to 2.9, \( P < 0.0001 \)). Finally, the further addition of C-reactive protein and fibrinogen (previously found to be associated with cardiovascular outcomes in this population-based cohort)\(^{28–30}\) to the model did not significantly change the association between segmental WM abnormalities and cardiovascular events (HR 2.0, 95% CI 1.4 to 2.9, \( P < 0.001 \)).

LV ejection fraction was also entered into the regression model that accounted for gender, age, waist-hip ratio, systolic blood pressure, diabetes mellitus, and global dysfunction.
blood pressure, diabetes mellitus, and segmental WM abnormalities. In this model, segmental WM abnormality was still associated with a 1.9-fold increased risk of first cardiovascular events (95% CI 1.3 to 2.8, \(P=0.001\)), independently of low ejection fraction (HR = 1.5 for ejection fraction <0.55 versus normal values, 95% CI 1.1 to 2.0, \(P=0.006\)).

In a separate analysis, the outcomes of the studied subgroups with or without WM abnormalities were compared with participants with prevalent CVD who were excluded from the primary analyses of the present study. Compared with subjects without prevalent CVD who had normal WM, the risks of cardiovascular events or cardiovascular death were >3-fold higher in participants without prevalent CVD who had WM abnormalities (\(P<0.0001\)) and >5-fold higher in participants with prevalent CVD (\(P<0.0001\); Figures 3 and 4).

**Prognostic Impact of Global WM Abnormalities.**

Similar to segmental WM abnormalities, first cardiovascular events and cardiovascular death were 2.2-fold and 2.7-fold more frequent in participants with global WM abnormalities than in those with normal WM (both \(P<0.0005\); Table 3). These associations were confirmed after adjustment for age, gender, waist/hip ratio, systolic blood pressure, and diabetes mellitus (Table 3). When ejection fraction was entered into the previous regression models, the risks of first cardiovascular event and cardiovascular mortality associated with global WM abnormalities did not retain statistical significance (both \(P=NS\)), whereas low ejection fraction did (HR 3.1, 95% CI 2.4 to 3.9 and HR 3.6, 95% CI 2.4 to 5.4, respectively; both \(P<0.0001\)).

**Discussion**

The present study demonstrates for the first time that echocardiographic detection of LV WM abnormalities in unscreened adults without clinically recognized CVD identifies a subgroup at intermediate risk of subsequent cardiovascular events and cardiovascular death between participants with prevalent CVD and those with neither recognized CVD nor abnormal WM. This finding is made more striking by the fact that it was obtained in a population-based cohort rather than in a group of clinical patients in whom echocardiographic evaluation could have been prompted by nonspecific symptoms.

**Prevalence and Correlates of WM Abnormalities**

The present study detected segmental and global WM abnormalities in 5% and 2%, respectively, of adults without known CVD. Gardin et al identified\(^{11}\) segmental WM abnormalities in 5.5% of a population of predominantly white adults aged 65 to 69 years and in 1.9% of a subset of participants with

![Figure 3. Rate of cardiovascular (CV) events (vertical axis) during follow-up (horizontal axis) in participants with WM abnormalities but no clinically recognized CVD (black continuous line), in those with neither WM abnormalities nor recognized CVD (gray continuous line), and in those with prevalent CVD (dotted line).](http://circ.ahajournals.org/content/152/15/e1116279.full)

![Figure 4. Rate of cardiovascular (CV) mortality (vertical axis) during follow-up (horizontal axis) in participants with WM abnormalities but no clinically recognized CVD (black continuous line), in those with neither WM abnormalities nor recognized CVD (gray continuous line), and in those with prevalent CVD (dotted line).](http://circ.ahajournals.org/content/152/15/e1116279.full)
neither ischemic heart disease nor hypertension in the Cardiovascular Health Study. The present study included hypertensive individuals but identified segmental or global WM abnormalities in 3.6% and 1.4% of normotensive participants, respectively. Consistent with the present findings, Gardin et al. found WM abnormalities to be more common in men and in hypertensive participants. In the present study, segmental WM abnormalities were associated with the presence of diabetes mellitus. These results are consistent with previous observations from the SHS of an association of abnormal global LV function with diabetes mellitus. Adults with segmental LV dysfunction had lower body mass index than participants with normal or globally abnormal LV function. This association persisted after adjustment for difficulty of echocardiographic imaging, which is consistent with the previously reported association between LV systolic dysfunction and reduction of body mass index in participants with LV dysfunction.

The present study also documented associations of both segmental and global WM abnormalities with measures of preclinical CVD, including elevated LV mass index and albuminuria. Moreover, levels of fibrinogen and C-reactive protein, markers of inflammation that predict incident cardiovascular events and death in population-based cohorts, were higher in participants with WM abnormalities, but this did not affect the increased likelihood of cardiovascular events associated with WM abnormalities.

**WM Abnormalities and Prediction of Cardiovascular Outcome**

The relation of segmental WM abnormalities to cardiovascular events has been demonstrated previously in acute ischemic heart disease and CHF. Moller et al. recently confirmed that regional WM abnormalities assessed immediately after an acute MI independently predict death and hospitalization for CHF. The present study extends these observations by demonstrating that WM abnormalities also predict subsequent clinical cardiovascular events in an elected population of adults without recognized CVD. Of note, the rates of cardiovascular events and cardiovascular death in participants with WM abnormalities but without clinically recognized CVD were closer to the rates in individuals excluded from the present study because of prevalent CVD than to the rates detected in participants without overt CVD who had normal LV WM.

In the relatively normal clinical conditions found in the present study population, incidentally detected WM abnormalities can be related to transient ischemic dysfunction, myocardial scar, stunning/hibernation, cardiomyopathy, or different combinations of these conditions. In particular, epidemiological studies have established that a number of MIs (from 5% to as many as 20% in reports from Framingham) go undetected at the time of occurrence. In a previous report, indirect ECG evidence of clinically unrecognized MI predicted subsequent cardiovascular events, but assessment of LV WM was unavailable in that study.

In addition, previous studies suggest that the long-term cardiovascular prognosis of individuals with silent MI may be similar to that of subjects with recognized MI. Individuals with ECG Q waves, the most commonly used method to detect unrecognized MIs, have been excluded from the present analysis, but this would not rule out all silent MIs, because imaging studies have greater sensitivity for detecting transmural or partial-thickness scar than do ECG Q waves.

Detection of segmental LV WM abnormality improved risk stratification even after adjustment for the effect of low LV ejection fraction in the present analyses. Consistent with the present observation, regional WM abnormality was found to be more important than global LV systolic function for predicting adverse cardiovascular events in patients receiving thrombolytic therapy for ST-elevation MI. In the present study, segmental WM abnormality predicted cardiovascular outcome independent of level of ejection fraction, consistent with the presence of normal global LV ejection fraction in nearly 60% of SHS participants with segmental WM abnor-

### TABLE 3. Cumulative Incidence and HRs of All Cardiovascular Events and Cardiovascular Death in Participants With Global WM Abnormalities

<table>
<thead>
<tr>
<th>End Points</th>
<th>Rate*</th>
<th>No. (%)</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular events</td>
<td>60.2</td>
<td>13 (32.5)</td>
<td>2.2 (1.3–3.8)</td>
<td>2.4 (1.4–4.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Single components</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>6.6</td>
<td>2 (5.0)</td>
<td>1.1 (0.4–3.5)</td>
<td>1.0 (0.3–3.2)</td>
<td>0.97</td>
</tr>
<tr>
<td>Stroke</td>
<td>3.2</td>
<td>1 (2.5)</td>
<td>3.1 (1.0–10.0)</td>
<td>3.1 (1.0–9.8)</td>
<td>0.06</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>22.1</td>
<td>6 (15.0)</td>
<td>2.1 (1.1–4.2)</td>
<td>1.9 (0.9–3.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>Heart failure</td>
<td>10.1</td>
<td>3 (7.5)</td>
<td>2.9 (1.4–6.3)</td>
<td>3.1 (1.5–6.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>17.9</td>
<td>5 (12.5)</td>
<td>2.7 (1.2–6.1)</td>
<td>3.4 (1.5–7.7)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*Per 1000 patient-years of follow-up.
†Models adjusted for age, gender, waist-hip ratio, systolic blood pressure, diabetes mellitus, and segmental WM abnormalities.
‡Compared with participants with normal WM (data in Table 2).
malities. In addition, LV ejection fraction is a measure of global LV chamber function that summates the contraction of different regions, therefore allowing hyperkinetic segments to offset the effect of hypokinetic ones.

Study Limitations
Some of the present study should be considered. First, this study was undertaken in a population with high prevalences of diabetes mellitus and obesity, and the results may not be generalizable to other populations; however, LV WM abnormalities were detected by similar echocardiographic methods in an even higher proportion (1/8) of ambulatory hypertensive patients with ECG LV hypertrophy who had substantially lower mean body mass index.24 Second, echocardiograms were recorded before introduction of harmonic imaging or newer methods for quantitative assessment of regional systolic function. Thus, future study of the magnitude and timing of segmental LV contraction in population-based samples will be needed to understand the relative contribution of delayed contraction versus reduced or absent absolute contraction to segmental WM abnormalities in asymptomatic adults. Finally, B-type natriuretic peptide levels were measured in only 897 participants (29%) from a single center in the present study, which precludes their inclusion in the present analyses.

Conclusions
The present population-based study of adults without clinically evident CVD demonstrates a strong relationship between the presence of WM abnormalities and cardiovascular events and death. These findings suggest that echocardiographic assessment of regional LV dysfunction can identify adults without known CVD who are at increased risk of future cardiovascular events.

Sources of Funding
This study was supported in part by grants HL-41642, HL-41652, HL-41664, HL-65521, and M10-RR0047-34 (General Clinical Research Center) from the National Institutes of Health, Bethesda, Md.

Disclosures
None.

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**CLINICAL PERSPECTIVE**

In the Strong Heart Study, a large, population-based study, the prognostic value of echocardiographic left ventricular wall motion (WM) abnormalities was evaluated in 2864 participants without clinically recognizable cardiovascular disease. Relationships between WM abnormalities and fatal and nonfatal cardiovascular events (including myocardial infarction, stroke, coronary artery disease, and heart failure; n=554) and cardiovascular death (n=182) during 8±2 years follow-up were examined. In Cox regression, after adjustment for age, gender, waist/hip ratio, systolic blood pressure, and diabetes mellitus, segmental WM abnormalities were associated with a 2.5-fold higher risk of cardiovascular events and a 2.6-fold higher risk of cardiovascular death (both P<0.0001). In similar multivariable models, global WM abnormalities were associated with a 2.4-fold higher risk of cardiovascular events (P=0.001) and a 3.4-fold higher risk of cardiovascular death (P=0.003). These results demonstrate that echocardiographic left ventricular WM abnormalities in adults without overt cardiovascular disease predict 2- to 3.5-fold higher risks of cardiovascular morbidity and mortality, independent of established risk factors. Thus, detection of regional left ventricular dysfunction by echocardiography, and probably by other techniques, strongly predicts cardiovascular events and death. Given the adverse prognosis of echocardiographic evidence of regional left ventricular dysfunction in adults without established cardiovascular disease, it may be prudent to treat established cardiovascular risk factors in these individuals more intensively. Whether individuals with regional left ventricular dysfunction would benefit from additional evaluation to identify asymptomatic coronary artery disease or early cardiomyopathy requires further study.
Prevalence and Prognostic Significance of Wall-Motion Abnormalities in Adults Without Clinically Recognized Cardiovascular Disease: The Strong Heart Study
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Circulation. 2007;116:143-150; originally published online June 18, 2007;
doi: 10.1161/CIRCULATIONAHA.106.652149
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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