Relations of Insulin Resistance and Glycemic Abnormalities to Cardiovascular Magnetic Resonance Measures of Cardiac Structure and Function

The Framingham Heart Study

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Background—Data regarding the relationships of diabetes, insulin resistance, and subclinical hyperinsulinemia/hyperglycemia with cardiac structure and function are conflicting. We sought to apply volumetric cardiovascular magnetic resonance (CMR) in a free-living cohort to potentially clarify these associations.

Methods and Results—A total of 1603 Framingham Heart Study Offspring participants (age, 64±9 years; 55% women) underwent CMR to determine left ventricular mass (LVM), LVM to end-diastolic volume ratio (LVM/LVEDV), relative wall thickness (RWT), ejection fraction, cardiac output, and left atrial size. Data regarding insulin resistance (homeostasis model, HOMA-IR) and glycemia categories (normal, impaired insulinemia or glycemia, prediabetes, and diabetes) were determined. In a subgroup (253 men, 290 women) that underwent oral glucose tolerance testing, we related 2-hour insulin and glucose with CMR measures. In both men and women, all age-adjusted CMR measures increased across HOMA-IR quartiles, but multivariable-adjusted trends were significant only for LVM/h2.7 and LVM/LVEDV. LVM/LVEDV and RWT were higher in participants with prediabetes and diabetes (in both sexes) in age-adjusted models, but these associations remained significant after multivariable adjustment only in men. LVM/LVEDV was significantly associated with 2-hour insulin in men only, and RWT was significantly associated with 2-hour glucose in women only. In multivariable stepwise selection analyses, the inclusion of body mass index led to a loss in statistical significance.

Conclusions—Although insulin and glucose indices are associated with abnormalities in cardiac structure, insulin resistance and worsening glycemia are consistently and independently associated with LVM/LVEDV. These data implicate hyperglycemia and insulin resistance in concentric LV remodeling. (Circ Cardiovasc Imaging. 2010;3:257-263.)

Key Words: insulin resistance | diabetes | left ventricular mass | left ventricular remodeling | cardiovascular MRI | glycemia

Diabetes is an important risk factor for heart failure. One potential mechanism for the predisposition to heart failure in people with diabetes is the direct toxic effect of hyperinsulinemia and hyperglycemia on cardiomyocytes and the surrounding interstitium, leading to maladaptive changes in cardiac structure and function that antedate the development of clinical heart failure. Several investigators have examined the associations of abnormalities in insulin and glucose metabolism (eg, insulin resistance, impaired fasting glucose) in individuals without overt diabetes to indices of cardiac structure and function7-12 and heart failure.13 Many prior studies have been inconsistent, reporting both a positive association7,10,11 and a lack of association.8,9,12 These previous studies have largely used transthoracic echocardiographic measures for cardiac structural measurements. Two-dimensional echocardiography is a widely available noninvasive technology. However, echocardiography leads to exclusion of many older subjects and those with higher body mass index (BMI) due to inadequate echocardiograph quality, thereby limiting evaluation of all age groups and the full range of BMI in the population.

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Cardiovascular MRI (CMR) provides a volumetric assessment of cardiac structure and function with successful acquisitions of highly accurate and reproducible datasets, including...
determination of left ventricular (LV) concentricity, in nearly all subjects. Application of CMR (or other volumetric methods) may therefore facilitate more accurate analysis of the associations of glycemia indices and cardiac measures. We sought to apply CMR methods to further elucidate the potential relationship of increasing insulin resistance, elevated levels of insulin and glucose with cardiac structure, and to determine if the presence of prediabetes and diabetes is associated with alterations of cardiac structure and function compared to the presence of normal insulin and glucose measures.

Methods

Study Sample and Design

The design and characteristics of the Framingham Heart Study Offspring cohort have been described elsewhere. Briefly, members of the Offspring cohort, (comprising the 5124 children of the original cohort and their spouses) were enrolled in 1971 and have been evaluated approximately every 4 years (“examination cycles”). Examination cycle 7, attended by 3799 participants during the years 1998 to 2001, constituted the sampling frame for this study. Among cycle 7 attendees, 1794 participants with normal sinus rhythm and no contraindications to CMR imaging underwent a CMR study between the years 2002 and 2005 and had contemporaneous fasting glucose and insulin levels available. Participants with an incomplete or poor-quality CMR and participants with clinical coronary insufficiency, myocardial infarction, or heart failure, were excluded. The remaining 1603 individuals formed the sample for this study. Participants provided written informed consent for CMR and cycle 7 examinations and testing. The study was approved by the Institutional Review Boards of Boston Medical Center and Beth Israel Deaconess Medical Center.

Assessment of Glucose and Insulin Levels and Insulin Resistance

Baseline samples for glucose and insulin were drawn after an overnight fast. In a stratified subsample, we also obtained measurements 2 hours after a 75-g glucose load administered to fasting participants (2-hour insulin and 2-hour glucose).

Glucose measurements were performed with a hexokinase reagent kit (Roche Diagnostics, Indianapolis, Ind). Insulin measurements were done by radioimmunoassay (Trinity Biotech, St Louis, Mo). The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated as: HOMA-IR = fasting glucose (mmol/L) × fasting insulin (µU/mL)/22.5. Both elevated fasting glucose and fasting insulin predict incident diabetes. Fasting insulin is highly correlated with HOMA-IR, and a threshold of 75th percentile has been previously described as identifying those with insulin resistance and increased risk for cardiovascular disease. Therefore, we used a fasting plasma glucose threshold of 100 mg/dL and a fasting plasma insulin threshold of 75th percentile to classify participants into a spectrum of worsening glycemic milieu as follows: (1) diabetes (n=122), including those with a fasting plasma glucose ≥126 mg/dL or receiving insulin or other hypoglycemic therapy; (2) prediabetes (n=176), for those without diabetes but with both fasting glucose ≥100 mg/dL and fasting insulin >75th percentile of distribution; (3) impaired insulinemia/glycemia (n=442) included those participants with either fasting insulin >75th percentile of distribution or fasting glucose >100 mg/dL (but not both); and (4) normal (n=863), including those with both fasting glucose ≤100 mg/dL and fasting insulin ≤75th percentile of distribution.

Definition of Covariates

Data for covariates were obtained from the contemporaneous examination cycle. Blood pressure was calculated using the average of 2 auscultated measurements performed while seated. Hypertension was defined as a systolic blood pressure >140 mm Hg or a diastolic blood pressure >90 mm Hg or receiving antihypertensive therapy. “Cardioactive drugs” were defined as agents with consistent evidence for favorable effects on LV remodeling, and they include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or aldosterone antagonists. Smoking status was defined as regular smoking in the year preceding the examination.

CMR Methods and Definition of Cardiac Measures

Cine CMR images were acquired with subjects in the supine position on a 1.5-T CMR scanner (Gyrosan ACS/NT, Phillips Medical Systems, Best, The Netherlands) using a 5-element cardiac array receiver coil. Eight to 12 contiguous 10-mm-thick LV short-axis images were acquired using an ECG-gated, steady-state free precession sequence, with a 30 to 40 ms temporal resolution and 1.92×1.56 mm² in-plane spatial resolution, during a series of end-tidal breath holds.

Epicardial (end-diastolic) and endocardial (end-diastolic and end-systolic) borders were manually traced by a blinded expert observer (C.J.S.) using an EasyScil workstation (Phillips Medical Systems). LV end-diastolic and end-systolic volumes (EDV and ESV) were calculated integrating over multiple slices using the summation of discs method. LV mass (LVM) was calculated by multiplying diastolic LV myocardial volume with density of myocardium (1.05 g/mL), and indexed to height². We divided LVM by LVEDV to obtain the LVM/LVEDV ratio (also known as concentricity). LV ejection fraction (EF) was calculated as (EDV−ESV)/EDV. Cardiac output was calculated as (EDV−ESV)×heart rate. LV end-diastolic dimension (LVEDD) and infarcted wall thickness (ILWT) were measured in end-diastole from a short-axis frame immediately basal to the tip of papillary muscle tips. Relative wall thickness (RWT) was calculated as 2×ILWT/LVEDD.

Statistical Analysis

We compared men and women with regard to categorical clinical variables using the χ² test. For continuous clinical variables and for CMR measures, we compared the sexes using the t test. In our prespecified primary analysis, we related sex-specific quartiles of HOMA-IR and glycemia categories to CMR measures. We used sex-specific ANCOVA to assess trends in adjusted means of CMR measures across glycemia categories and HOMA-IR quartiles in a 2-step fashion: Step 1 adjusted for age alone and step 2 adjusted jointly for age, systolic blood pressure, BMI, smoking status, and use of cardioactive drugs.

In secondary analyses, we related quartiles of 2-hour glucose and 2-hour insulin with CMR measures in the subgroup of participants who underwent oral glucose tolerance testing. Finally, we performed multivariable stepwise selection analysis relating HOMA-IR and glycemia categories to CMR measures to elucidate the significant covariates contributing to the associations.

Results are presented as trends in adjusted mean values for CMR measures with a test for linear trend. We individually tested for linear trend between the quartiles of HOMA-IR and glycemic categories with the CMR measures by entering the quartile or category (coded 0, 1, 2, and 3) as a continuous variable in the ANCOVA model. The test for linear trend comprised of the 1 degree of freedom t test for the quartile. A significant linear trend test implies the trajectory of the CMR measure increases or decreases with increasing HOMA-IR quartile or glycemic category. Conversely, a nonsignificant trend test implies there is no decreasing or increasing trajectory across quartile categories. All analyses were performed with SAS version 8.1 (SAS Institute, Cary, NC). A 2-sided probability value of 0.05 was used to ascertain statistical significance.

Results

Clinical and biochemical characteristics and summary statistics of CMR measures by sex are shown in Table 1. Mean age for the entire group was 64±9 years. Men had a higher BMI and greater prevalence of hypertension compared with women. Nine percent of men and 6% of women had diabetes.
Normal groups are presented in Table 3. In age-adjusted analyses, we observed that CMR measures were lowest in the normal group, intermediate in the impaired insulinenia/glycemia group, and highest in the prediabetes and diabetes groups. These trends were statistically significant (P<0.005) in age-adjusted analyses for all CMR measures in both sexes except for EF. Participants with prediabetes had similar elevations in CMR measures compared with those with diabetes. On multivariable adjustment, these associations were not statistically significant in women. However, in men, both LVM/LVEDV and RWT continued to demonstrate a modest but significant increasing trend even after multivariable adjustment. The associations of LAD, LVM/ht².⁷, EF, and CO were not statistically significant after multivariable adjustment.

Relations of 2-Hour Insulin to CMR Measures
When relations of 2-hour insulin to CMR measures were evaluated in women, we found a pattern similar to that observed with the glycemia categories, whereas adjusted means of CMR measures increased across quartiles of 2-hour insulin, the relations were not statistically significant after multivariable adjustment (Supplementary Table 2). In men, covariate-adjusted mean LVM/LVEDV increased significantly across increasing quartiles of 2-hour insulin in multivariable adjusted analyses. Associations of LAD, LVM/ht².⁷, RWT, EF, and CO with 2-hour insulin were not statistically significant in men.

Relations of 2-Hour Glucose to CMR Measures
In men, we observed an increasing trend of LVM/LVEDV, RWT, and CO across quartiles of 2-hour glucose, in age-adjusted analyses. Associations of LAD, LVM/ht².⁷, EF, and CO were not statistically significant even after multivariable adjustment.
adjusted but not in multivariable adjusted models (Supplementary Table 3). LAD, LVM/ht².7, and EF were not associated with 2-hour glucose in men. In women, we observed that only RWT was significantly associated with 2-hour glucose in multivariable adjusted models (Supplementary Table 3).

**Stepwise Selection Analyses**

We performed stepwise selection including 1 covariate at a time in the multivariable models. We observed that in those multivariable analyses relating HOMA-IR and glycemia categories to CMR measures that were nonsignificant, glycemia measures lost statistical significance observed in the age-adjusted analyses on inclusion of BMI.

**Discussion**

**Principal Findings**

In this middle-aged to elderly community-based cohort, we demonstrate that higher levels of HOMA-IR are associated with increasing LVM/ht².7 and LVM/LVEDV in both sexes. On multivariable adjustment (especially BMI), the trend in LVM/ht².7 is reversed, suggesting that the association between insulin resistance and LVM/ht².7 is modified by covariates (mainly BMI). The direction and significance of association between HOMA-IR and LVM/LVEDV was unchanged by multivariable adjustment, suggesting a graded increase in concentricity with increasing insulin resistance. We also observed a graded increase in LVM/LVEDV and RWT across glycemia categories in men but not in women. Associations of 2-hour insulin and glucose with CMR measures in women were similar to those seen with glycemia categories; however, in men, increasing concentricity continued to be a significant correlate of 2-hour insulin.

An intriguing finding of our investigation is the consistent association between glycemic abnormalities and ventricular concentricity (LVM/LVEDV), only in men. Adjustment for BMI caused a loss of statistical significance for this relation.
ship only in the ANCOVA evaluating 2-hour glucose. This suggests that both rising HOMA-IR and movement into a worse glycemia category may influence ventricular remodeling, independent of other correlates of concentricity such as blood pressure and BMI. Our study thus extends the findings of prior investigations that reported increased prevalence of concentric remodeling in those with diabetes, insulin resistance, and glucose intolerance.\textsuperscript{12}

Comparison to Previous CMR Literature

Two prior investigations using a different segmented k-space gradient echo CMR imaging sequence evaluated participants from the Multi-ethnic Study of Atherosclerosis (MESA) and reported on the associations of glycemia indices to CMR measures of absolute LVM and LVEDV. Bertoni et al\textsuperscript{27} observed that in multivariable-adjusted analyses, participants with diabetes and impaired fasting glucose did not have a significantly higher LVM but had significantly lower LVEDV. In a subsequent MESA report, Heckbert et al\textsuperscript{28} reported that participants with diabetes had a higher LVM and lower LVEDV, whereas participants with impaired fasting glucose had a lower LVEDV compared with those with normal glucose tolerance. Although neither study reported LVM/LVEDV, their findings that are consistent with an association of increased concentricity with diabetes and glycemic abnormalities. In our study, we directly assessed LVM/LVEDV in a comprehensive set of analyses evaluating its relationship to insulin resistance, glycemia categories, and 2-hour insulin and glucose. When we evaluated the individual components of LVM/LVEDV, we observed a decreasing trend in LVEDV across quartiles of HOMA-IR (Supplementary Table 4) and categories of glycemia (Supplementary Table 5) consistent with those reported from MESA by Bertoni et al and Heckbert et al. Thus, our findings confirm and extend those from previous CMR literature and add to the literature assessing relations of glycemia to cardiac measures using echocardiography, with which estimates of

Table 3. Adjusted CMR Measures by Glycemia Categories

<table>
<thead>
<tr>
<th>Men Models</th>
<th>Normal (n=330)</th>
<th>High FPG/FPI (n=235)</th>
<th>Prediabetes (n=92)</th>
<th>Diabetes (n=68)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD, mm</td>
<td>Age-adjusted</td>
<td>31</td>
<td>32</td>
<td>33</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>32</td>
<td>32</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>LVM/ht\textsuperscript{2.7}, g/m\textsuperscript{2.7}</td>
<td>Age-adjusted</td>
<td>27.2</td>
<td>28.2</td>
<td>30.2</td>
<td>29.9</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>28.3</td>
<td>27.7</td>
<td>28.4</td>
<td>28.5</td>
</tr>
<tr>
<td>LVM/LVEDV, g/mL</td>
<td>Age-adjusted</td>
<td>0.87</td>
<td>0.90</td>
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<td></td>
<td>MV-adjusted</td>
<td>0.88</td>
<td>0.89</td>
<td>0.97</td>
<td>0.90</td>
</tr>
<tr>
<td>RWT</td>
<td>Age-adjusted</td>
<td>0.28</td>
<td>0.29</td>
<td>0.30</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>0.28</td>
<td>0.29</td>
<td>0.30</td>
<td>0.29</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>Age-adjusted</td>
<td>5.8</td>
<td>5.9</td>
<td>6.1</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>5.9</td>
<td>5.9</td>
<td>5.8</td>
<td>6.0</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>Age-adjusted</td>
<td>65</td>
<td>66</td>
<td>67</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>66</td>
<td>66</td>
<td>67</td>
<td>64</td>
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</table>

<table>
<thead>
<tr>
<th>Women Models</th>
<th>Normal (n=533)</th>
<th>High FPG/FPI (n=207)</th>
<th>Prediabetes (n=84)</th>
<th>Diabetes (n=54)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD, mm</td>
<td>Age-adjusted</td>
<td>28</td>
<td>29</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>28</td>
<td>29</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>LVM/ht\textsuperscript{2.7}, g/m\textsuperscript{2.7}</td>
<td>Age-adjusted</td>
<td>22.7</td>
<td>24.0</td>
<td>26.6</td>
<td>25.0</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>23.7</td>
<td>23.2</td>
<td>23.8</td>
<td>22.7</td>
</tr>
<tr>
<td>LVM/LVEDV, g/mL</td>
<td>Age-adjusted</td>
<td>0.79</td>
<td>0.80</td>
<td>0.85</td>
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<td>MV-adjusted</td>
<td>0.80</td>
<td>0.80</td>
<td>0.82</td>
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<tr>
<td>RWT</td>
<td>Age-adjusted</td>
<td>0.25</td>
<td>0.26</td>
<td>0.27</td>
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<tr>
<td></td>
<td>MV-adjusted</td>
<td>0.26</td>
<td>0.26</td>
<td>0.26</td>
<td>0.26</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>Age-adjusted</td>
<td>4.7</td>
<td>5.0</td>
<td>5.3</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>4.8</td>
<td>4.8</td>
<td>4.9</td>
<td>4.9</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>Age-adjusted</td>
<td>69</td>
<td>69</td>
<td>70</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>69</td>
<td>69</td>
<td>69</td>
<td>68</td>
</tr>
</tbody>
</table>

Mean values of LV measures are given.
MV-adjusted indicates multivariable-adjusted; MV model adjusted for age, BMI, systolic blood pressure, cardioactive drug therapy, and smoking status.

*Normal* group includes participants with both fasting plasma glucose $\leq$100 mg/dL and fasting plasma insulin $\leq$75th percentile of distribution; "High FPG/FPI" group includes those with either fasting plasma insulin $>75$th percentile of distribution or fasting plasma glucose $>100$ mg/dL (but not both); and "prediabetes" includes those without diabetes but with both fasting plasma glucose $>100$ mg/dL and fasting plasma insulin $>75$th percentile of distribution.

*P value for linear trend.
evaluated 3D volumetric change are limited by greater variability.

**Contrasts With Prior Echocardiography Literature**

As noted previously, investigations relating glycemic abnormalities to transthoracic echocardiographic measures of cardiac structure and function reported conflicting results. In a previous Framingham Heart Study report, Rutter et al.\(^\text{10}\) noted increasing LVM with worsening glycemia status (but not with insulin resistance) that was more striking in women. The effect was largely attenuated by adjustment for BMI. In contrast, Devereux et al.\(^\text{29}\) evaluated 1542 hypertensive participants without diabetes and did not observe any associations between insulin and LVM. In studies evaluating insulin resistance measured via hyperinsulinemic-euglycemic clamp, Olsen et al.\(^\text{10}\) noted no associations with LV hypertrophy or other structural measures, whereas Paolisso et al.\(^\text{18}\) found a weak association with LV wall thickness. One limitation of studies using transthoracic echocardiography is the increased likelihood of exclusion of older and more obese subjects,\(^\text{10}\) thereby limiting the ability to clearly evaluate the associations of glycemia indices and LV structural measures.

**Mechanisms Underlying the Associations**

Experimental evidence and observations in humans implicate hyperglycemia, hyperinsulinemia, and impaired responses to a glucose load in ventricular remodeling. Experimentally induced hyperinsulinemia in rats leads to increased body mass, relative myocardial mass and blood pressure, and lower cardiac output\(^\text{31}\) and also causes characteristic changes in angiotensin receptor expression leading to modulation of ventricular remodeling responses to blood pressure.\(^\text{32}\) Panagia et al.\(^\text{33}\) reported that db/db mice (an animal model of type 2 diabetes) had lower cardiac output and impaired postischemic recovery compared with control mice. Similarly, serial CMR measurements in db/db mice demonstrate a progressive increase in LVM and RWT followed by a later increase in LV end-diastolic dimension and decrease in contractile function.\(^\text{34}\) Potential molecular mechanisms underlying the effects of insulin and glucose on the myocardium in humans are extensively reviewed elsewhere.\(^\text{35–37}\)

**Limitations**

Our study has several limitations. We used a cross-sectional design in a middle-aged to elderly Caucasian population that limits our ability to draw causal inferences or generalize to other age or ethnic groups. We had a single measurement of insulin and glucose; longitudinal measures may be more reflective of the effects on the heart. Finally, only a third of our cohort had oral glucose tolerance test results available, limiting our ability to fully evaluate the relations of 2-hour insulin and glucose to CMR measures.

**Conclusions**

In a free-living adult population without clinical coronary disease, we observed a fairly consistent association of abnormalities in insulin and glucose levels and insulin resistance with LVM/LVEDV, and we found that LVM/LVEDV was consistently associated with hyperglycemia and insulin resistance in multivariable analyses. However, the associations of diabetes, insulin resistance, and subclinical glycemia abnormalities with LVM/ht\(^\text{2,7}\) and other structural and functional abnormalities were primarily mediated by elevated BMI. These data suggest an important role for hyperglycemia and insulin resistance in concentric LV remodeling.

**Sources of Funding**

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**Disclosures**

None.

**References**


Glycemic Alterations and Cardiac Abnormalities

Prior studies evaluating the associations of diabetes, insulin resistance, and subclinical hyperinsulinemia/hyperglycemia with abnormal cardiac structure and function reported conflicting results. Cardiovascular magnetic resonance provides accurate volumetric measurements and may help clarify these relations. Because cardiac remodeling precedes and predicts cardiovascular disease, such biological insights may help in risk stratification or elucidation of therapeutic targets. We used sex-specific, multivariable-adjusted ANCOVA models to evaluate the associations of insulin resistance (assessed by the homeostasis model assessment [HOMA-IR]) and of glycemia categories of fasting plasma glucose and insulin with cardiovascular magnetic resonance measures of cardiac structure and function (left atrial dimension, left ventricular [LV] mass, LV mass-to–end-diastolic volume ratio, relative wall thickness, cardiac output, and ejection fraction) in a large cohort of free-living individuals without prevalent cardiovascular disease. In age-adjusted models in both men and women, we observed that HOMA-IR was significantly and positively related to all the cardiac indices; glycemia categories were similarly associated with all cardiac measures except ejection fraction. In multivariable models, LV mass/LV end-diastolic volume was the major correlate of both HOMA-IR and glycemia categories, whereas associations of other cardiac measures and glucose/insulin metabolism were mediated by body mass index. Our observations provide additional evidence for an important role for insulin resistance and glycemic alterations in influencing LV remodeling in individuals free of overt cardiovascular disease, and we also confirm the important role of body mass index in mediating associations of metabolic abnormalities with cardiac remodeling.

**CLINICAL PERSPECTIVE**

Prior studies evaluating the associations of diabetes, insulin resistance, and subclinical hyperinsulinemia/hyperglycemia with abnormal cardiac structure and function reported conflicting results. Cardiovascular magnetic resonance provides accurate volumetric measurements and may help clarify these relations. Because cardiac remodeling precedes and predicts cardiovascular disease, such biological insights may help in risk stratification or elucidation of therapeutic targets. We used sex-specific, multivariable-adjusted ANCOVA models to evaluate the associations of insulin resistance (assessed by the homeostasis model assessment [HOMA-IR]) and of glycemia categories of fasting plasma glucose and insulin with cardiovascular magnetic resonance measures of cardiac structure and function (left atrial dimension, left ventricular [LV] mass, LV mass-to–end-diastolic volume ratio, relative wall thickness, cardiac output, and ejection fraction) in a large cohort of free-living individuals without prevalent cardiovascular disease. In age-adjusted models in both men and women, we observed that HOMA-IR was significantly and positively related to all the cardiac indices; glycemia categories were similarly associated with all cardiac measures except ejection fraction. In multivariable models, LV mass/LV end-diastolic volume was the major correlate of both HOMA-IR and glycemia categories, whereas associations of other cardiac measures and glucose/insulin metabolism were mediated by body mass index. Our observations provide additional evidence for an important role for insulin resistance and glycemic alterations in influencing LV remodeling in individuals free of overt cardiovascular disease, and we also confirm the important role of body mass index in mediating associations of metabolic abnormalities with cardiac remodeling.
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SUPPLEMENTAL MATERIAL: Relations of Insulin Resistance and Glycemic Abnormalities to Cardiovascular Magnetic Resonance Measures of Cardiac Structure and Function: the Framingham Heart Study

I. Relations of HOMA-IR (as a continuous variable) to CMR measures
II. Relations of 2-hr insulin to CMR measures
III. Relations of 2-hr glucose to CMR measures
IV. Relations of HOMA-IR to LVM and LVEDV separately
V. Relations of glycemia categories to LVM and LVEDV separately
Supplementary Table 1: Relations of HOMA-IR to CMR measures

<table>
<thead>
<tr>
<th>Model</th>
<th>Beta estimate (SE)*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MEN</strong></td>
<td></td>
<td></td>
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<tr>
<td>LAD, mm</td>
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<td>Age-adjusted</td>
<td>1.03 (0.31)</td>
<td>0.0008</td>
</tr>
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<td>MV-adjusted</td>
<td>-0.97 (0.32)</td>
<td>0.002</td>
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<td>LVM/ht^{2.7}, g/m^{2.7}</td>
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<td></td>
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<tr>
<td>Age-adjusted</td>
<td>1.76 (0.33)</td>
<td>&lt;0.0001</td>
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<tr>
<td>MV-adjusted</td>
<td>-0.31 (0.34)</td>
<td>0.36</td>
</tr>
<tr>
<td>LVM/LVEDV, gm/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>0.07 (0.01)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MV-adjusted</td>
<td>0.05 (0.01)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RWT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>0.02 (0.003)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MV-adjusted</td>
<td>0.01 (0.003)</td>
<td>0.004</td>
</tr>
<tr>
<td>CO, L/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>0.24 (0.07)</td>
<td>0.001</td>
</tr>
<tr>
<td>MV-adjusted</td>
<td>-0.07 (0.08)</td>
<td>0.35</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.31 (0.41)</td>
<td>0.002</td>
</tr>
<tr>
<td>MV-adjusted</td>
<td>1.01 (0.47)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>WOMEN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD, mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.66 (0.23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MV-adjusted</td>
<td>-0.32 (0.23)</td>
<td>0.18</td>
</tr>
<tr>
<td>LVM/ht^{2.7}, g/m^{2.7}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.48 (0.23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MV-adjusted</td>
<td>-0.55 (0.23)</td>
<td>0.01</td>
</tr>
<tr>
<td>LVM/LVEDV, gm/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>0.03 (0.01)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MV-adjusted</td>
<td>0.01 (0.01)</td>
<td>0.03</td>
</tr>
<tr>
<td>RWT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>0.007 (0.003)</td>
<td>0.007</td>
</tr>
<tr>
<td>MV-adjusted</td>
<td>0.002 (0.003)</td>
<td>0.44</td>
</tr>
<tr>
<td>CO, L/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>0.32 (0.05)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MV-adjusted</td>
<td>-0.03 (0.05)</td>
<td>0.56</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>0.79 (0.29)</td>
<td>0.007</td>
</tr>
<tr>
<td>MV-adjusted</td>
<td>0.58 (0.34)</td>
<td>0.09</td>
</tr>
</tbody>
</table>
*Cells present beta coefficient estimates (standard error) for change in CMR measures (in their units) per standard deviation change in HOMA-IR.

MV-adjusted = multivariable-adjusted; CO = cardiac output; LAD = left atrial dimension; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVM = left ventricular mass; RWT = relative wall thickness

MV model adjusted for age, body mass index, systolic blood pressure, cardioactive drug therapy and smoking status.
### Supplementary Table 2: Adjusted CMR measures across 2-hr insulin quartiles

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Models</th>
<th>Quartile 1 (n = 66)</th>
<th>Quartile 2 (n = 64)</th>
<th>Quartile 3 (n = 63)</th>
<th>Quartile 4 (n = 62)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LAD, mm</strong></td>
<td></td>
<td>Age-adjusted</td>
<td>31</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MV-adjusted</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>30</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>LVM/ht^{g/m^2}, g/m^{2.7}</strong></td>
<td>Age-adjusted</td>
<td>27.6</td>
<td>27.9</td>
<td>27.0</td>
<td>29.1</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MV-adjusted</td>
<td>29.0</td>
<td>28.2</td>
<td>27.0</td>
<td>27.2</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>LVM/LVEDV, gm/ml</strong></td>
<td>Age-adjusted</td>
<td>0.86</td>
<td>0.87</td>
<td>0.87</td>
<td>0.97</td>
<td>0.0003</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>MV-adjusted</td>
<td>0.88</td>
<td>0.88</td>
<td>0.87</td>
<td>0.95</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>RWT</strong></td>
<td></td>
<td>Age-adjusted</td>
<td>0.27</td>
<td>0.28</td>
<td>0.28</td>
<td>0.30</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MV-adjusted</td>
<td>0.28</td>
<td>0.28</td>
<td>0.28</td>
<td>0.29</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>CO, L/min</strong></td>
<td></td>
<td>Age-adjusted</td>
<td>5.8</td>
<td>5.8</td>
<td>5.8</td>
<td>6.0</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MV-adjusted</td>
<td>6.0</td>
<td>5.8</td>
<td>5.8</td>
<td>5.7</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td></td>
<td>Age-adjusted</td>
<td>66</td>
<td>66</td>
<td>66</td>
<td>69</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MV-adjusted</td>
<td>66</td>
<td>66</td>
<td>66</td>
<td>68</td>
<td>0.64</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Models</th>
<th>Quartile 1 (n = 72)</th>
<th>Quartile 2 (n = 74)</th>
<th>Quartile 3 (n = 74)</th>
<th>Quartile 4 (n = 69)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LAD, mm</strong></td>
<td></td>
<td>Age-adjusted</td>
<td>27</td>
<td>28</td>
<td>28</td>
<td>30</td>
<td>0.0005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MV-adjusted</td>
<td>28</td>
<td>29</td>
<td>28</td>
<td>28</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>LVM/ht^{g/m^2}, g/m^{2.7}</strong></td>
<td>Age-adjusted</td>
<td>22.3</td>
<td>22.9</td>
<td>23.6</td>
<td>25.7</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MV-adjusted</td>
<td>23.9</td>
<td>23.8</td>
<td>23.2</td>
<td>23.4</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>LVM/LVEDV, gm/ml</strong></td>
<td>Age-adjusted</td>
<td>0.75</td>
<td>0.79</td>
<td>0.81</td>
<td>0.83</td>
<td>&lt;0.0001</td>
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<td>MV-adjusted</td>
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<td>0.80</td>
<td>0.80</td>
<td>0.81</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>RWT</strong></td>
<td></td>
<td>Age-adjusted</td>
<td>0.24</td>
<td>0.26</td>
<td>0.26</td>
<td>0.26</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
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<td>MV-adjusted</td>
<td>0.25</td>
<td>0.26</td>
<td>0.26</td>
<td>0.25</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>CO, L/min</strong></td>
<td></td>
<td>Age-adjusted</td>
<td>4.7</td>
<td>4.7</td>
<td>4.9</td>
<td>5.1</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MV-adjusted</td>
<td>4.9</td>
<td>4.9</td>
<td>4.9</td>
<td>4.6</td>
<td>0.80</td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td></td>
<td>Age-adjusted</td>
<td>67</td>
<td>69</td>
<td>71</td>
<td>71</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
<td></td>
<td>MV-adjusted</td>
<td>67</td>
<td>69</td>
<td>71</td>
<td>71</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Cells present mean values of cardiac measures; *p-value for trend.
MV-adjusted = multivariable-adjusted; CO = cardiac output; LAD = left atrial dimension; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVM = left ventricular mass; RWT = relative wall thickness

MV model adjusted for age, body mass index, systolic blood pressure, cardioactive drug therapy and smoking status.
### Supplementary Table 3: Adjusted CMR measures across 2-hr glucose quartiles

<table>
<thead>
<tr>
<th>Models</th>
<th>Quartile 1 (n = 67)</th>
<th>Quartile 2 (n = 67)</th>
<th>Quartile 3 (n = 63)</th>
<th>Quartile 4 (n = 58)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD, mm</td>
<td>Age-adjusted</td>
<td>31</td>
<td>32</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>31</td>
<td>32</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>LVM/ht²⁷, g/m²⁷</td>
<td>Age-adjusted</td>
<td>26.9</td>
<td>27.9</td>
<td>27.8</td>
<td>28.9</td>
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<tr>
<td></td>
<td>MV-adjusted</td>
<td>28.2</td>
<td>28.1</td>
<td>27.4</td>
<td>27.7</td>
</tr>
<tr>
<td>LVM/LVEDV, gm/ml</td>
<td>Age-adjusted</td>
<td>0.87</td>
<td>0.88</td>
<td>0.88</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>0.89</td>
<td>0.89</td>
<td>0.87</td>
<td>0.91</td>
</tr>
<tr>
<td>RWT</td>
<td>Age-adjusted</td>
<td>0.27</td>
<td>0.28</td>
<td>0.28</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>0.28</td>
<td>0.28</td>
<td>0.28</td>
<td>0.29</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>Age-adjusted</td>
<td>5.5</td>
<td>5.8</td>
<td>6.0</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>5.7</td>
<td>5.8</td>
<td>6.0</td>
<td>6.0</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>Age-adjusted</td>
<td>66</td>
<td>65</td>
<td>67</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>67</td>
<td>65</td>
<td>66</td>
<td>67</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD, mm</td>
<td>Age-adjusted</td>
<td>27</td>
<td>28</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>28</td>
<td>28</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>LVM/ht²⁷, g/m²⁷</td>
<td>Age-adjusted</td>
<td>21.3</td>
<td>23.0</td>
<td>25.2</td>
<td>25.0</td>
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<tr>
<td></td>
<td>MV-adjusted</td>
<td>23.2</td>
<td>23.5</td>
<td>24.1</td>
<td>23.5</td>
</tr>
<tr>
<td>LVM/LVEDV, gm/ml</td>
<td>Age-adjusted</td>
<td>0.75</td>
<td>0.79</td>
<td>0.82</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>0.78</td>
<td>0.80</td>
<td>0.80</td>
<td>0.80</td>
</tr>
<tr>
<td>RWT</td>
<td>Age-adjusted</td>
<td>0.24</td>
<td>0.27</td>
<td>0.26</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>0.25</td>
<td>0.27</td>
<td>0.26</td>
<td>0.25</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>Age-adjusted</td>
<td>4.5</td>
<td>4.8</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>4.8</td>
<td>4.9</td>
<td>4.8</td>
<td>4.8</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>Age-adjusted</td>
<td>69</td>
<td>69</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>70</td>
<td>69</td>
<td>70</td>
<td>69</td>
</tr>
</tbody>
</table>

Cells present mean values of cardiac measures; *p-value for trend.
MV-adjusted = multivariable-adjusted; CO = cardiac output; LAD = left atrial dimension; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVM = left ventricular mass; RWT = relative wall thickness

MV model adjusted for age, body mass index, systolic blood pressure, cardioactive drug therapy and smoking status.
### Supplementary Table 4: Adjusted LVM and LVEDV measures across HOMA-IR quartiles

<table>
<thead>
<tr>
<th></th>
<th>Models</th>
<th>Quartile 1 0.41-2.43† (n = 176)</th>
<th>Quartile 2 2.44-3.55† (n = 174)</th>
<th>Quartile 3 3.56-5.64† (n = 168)</th>
<th>Quartile 4 5.66-57.31† (n = 132)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVM, gm</td>
<td>Age-adjusted</td>
<td>124</td>
<td>125</td>
<td>126</td>
<td>134</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>131</td>
<td>127</td>
<td>124</td>
<td>126</td>
<td>0.04</td>
</tr>
<tr>
<td>LVEDV, ml</td>
<td>Age-adjusted</td>
<td>149</td>
<td>143</td>
<td>144</td>
<td>141</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>153</td>
<td>144</td>
<td>142</td>
<td>135</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Models</th>
<th>Quartile 1 0.23-2.03† (n = 216)</th>
<th>Quartile 2 2.04-2.84† (n = 213)</th>
<th>Quartile 3 2.85-4.25† (n = 208)</th>
<th>Quartile 4 4.26-43.01† (n = 175)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVM, gm</td>
<td>Age-adjusted</td>
<td>82</td>
<td>82</td>
<td>86</td>
<td>93</td>
<td>&lt;0.0001</td>
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<tr>
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<td>MV-adjusted</td>
<td>87</td>
<td>84</td>
<td>85</td>
<td>85</td>
<td>0.20</td>
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<td>LVEDV, ml</td>
<td>Age-adjusted</td>
<td>108</td>
<td>106</td>
<td>108</td>
<td>113</td>
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<tr>
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<td>MV-adjusted</td>
<td>112</td>
<td>108</td>
<td>108</td>
<td>105</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Cells present adjusted mean values of cardiac measures; *p-value for trend; †range of HOMA-IR for the respective quartile.

MV-adjusted = multivariable-adjusted; LVM = left ventricular mass; LVEDV = left ventricular end-diastolic volume.

MV model adjusted for age, body mass index, systolic blood pressure, cardioactive drug therapy and smoking status.
Supplementary Table 5: Adjusted LVM and LVEDV measures across glycemia categories

<table>
<thead>
<tr>
<th></th>
<th>Models</th>
<th>Normal (n = 330)</th>
<th>High FPG/FPI (n = 235)</th>
<th>Pre-Diabetes (n = 92)</th>
<th>Diabetes (n = 68)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVM</td>
<td>Age-adjusted</td>
<td>125</td>
<td>127</td>
<td>136</td>
<td>136</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>129</td>
<td>125</td>
<td>129</td>
<td>131</td>
<td>0.16</td>
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<tr>
<td>LVEDV</td>
<td>Age-adjusted</td>
<td>146</td>
<td>144</td>
<td>140</td>
<td>151</td>
<td>0.11</td>
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<tr>
<td></td>
<td>MV-adjusted</td>
<td>149</td>
<td>143</td>
<td>136</td>
<td>148</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVM</td>
<td>Age-adjusted</td>
<td>83</td>
<td>88</td>
<td>95</td>
<td>93</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>86</td>
<td>85</td>
<td>86</td>
<td>86</td>
<td>0.96</td>
</tr>
<tr>
<td>LVEDV</td>
<td>Age-adjusted</td>
<td>106</td>
<td>111</td>
<td>114</td>
<td>113</td>
<td>0.0002</td>
</tr>
<tr>
<td></td>
<td>MV-adjusted</td>
<td>109</td>
<td>109</td>
<td>107</td>
<td>107</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Cells present adjusted mean values of cardiac measures; *p-value for trend.

MV-adjusted = multivariable-adjusted; LVM = left ventricular mass; LVEDV = left ventricular end-diastolic volume. “Normal” group includes participants with both fasting plasma glucose ≤ 100mg/dl and fasting plasma insulin ≤ 75th percentile of distribution; “High FPI/FPG” group includes those with either fasting plasma insulin > 75th percentile of distribution or fasting plasma glucose > 100mg/dl (but not both); and “pre-diabetes” includes those without diabetes but with both fasting plasma glucose > 100mg/dl and fasting plasma insulin > 75th percentile of distribution.

MV model adjusted for age, body mass index, systolic blood pressure, cardioactive drug therapy and smoking status.