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Contribution of Central Adiposity to Left Ventricular Diastolic Function (From the Baltimore Longitudinal Study of Aging)

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Abstract

We examined relationships of central adiposity with left ventricular (LV) diastolic dysfunction in men and women who participated in the Baltimore Longitudinal Study of Aging, a prospective community-based study of older persons. The sample for this cross-sectional analysis included 399 women and 370 men. Central adiposity was estimated by waist circumference (WC) and global adiposity by body mass index (BMI). Using data from a comprehensive echocardiographic study that included tissue Doppler imaging, diastolic function was graded according to three parameters (E/A ratio, E/Em ratio and left atrial volume index). In logistic regression models adjusted for age, gender, cardiovascular risk factors and hemodynamic parameters, WC and BMI were both independently associated with LV diastolic dysfunction. However, when both WC and BMI were in the same model, only WC remained significantly associated with LV diastolic dysfunction (OR= 1.04, 95% CI: 1.01 to 1.08, p= 0.02). In gender stratified analyses, WC was found significantly associated with LV diastolic dysfunction - independently of BMI - in women (OR=1.08, 95% CI: 1.04 to 1.14, p<.001) but not in men (OR= 1.00, 95% CI: 0.95 to 1.05, p= 0.91). Further adjustment for left ventricular mass index failed to modify these relations. In conclusion, the adverse effect of central adiposity on LV diastolic function was independent of general adiposity and more pronounced among women. The impact of visceral adiposity on LV diastolic dysfunction would benefit from confirmation in longitudinal studies.

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Keywords

Diastolic dysfunction; adiposity; waist circumference; body mass index

INTRODUCTION

A number of studies have shown that measures of central adiposity such as waist circumference (WC) are superior to measures of global adiposity such as weight and body mass index (BMI) in assessing the risk of cardiovascular disease¹, and all-cause and cardiovascular-specific mortality². Waist circumference has also been independently associated with left ventricular (LV) diastolic dysfunction, evaluated using the ratio of early-to-late transmitral velocity (E/A ratio)^{3,4} or a semiquantitative categorical classification that combines multiple echocardiographic parameters beyond E/A ratio to define different patterns of LV diastolic dysfunction^{5,6}. However, the additive effect of WC over BMI on the grade of LV diastolic dysfunction remains unclear. In addition, as fat quantity and anatomical distribution is quite different in men and in women, the impact of body composition on LV diastolic function may be sex-specific but this hypothesis has not been previously tested. A better understanding of the link between central adiposity and LV diastolic dysfunction may help elucidate mechanisms through which adiposity contributes to the risk of cardiovascular morbidity and mortality⁷.

We evaluated the relation between waist circumference and BMI with LV diastolic dysfunction in Baltimore Longitudinal Study of Aging participants. We hypothesized that: i) central adiposity is the main mediator of the relationship between general adiposity and LV diastolic dysfunction, ii) the association of central adiposity with impaired LV relaxation is stronger than with other LV filling patterns, iii) the effect of central adiposity on LV diastolic dysfunction is different in men and women.

METHODS

The study sample is part of the Baltimore Longitudinal Study of Aging (BLSA), a prospective study of community-dwelling volunteers who undergo approximately 3 days of medical, physiological, and psychological examinations at regular intervals of about 3 years⁸. Healthy individuals have been recruited for the BLSA since its inception in 1957 according to rigid eligibility criteria. For the present cross-sectional analysis we considered 1140 participants who had a comprehensive echocardiographic study that included tissue Doppler imaging (TDI). Of these, we excluded 58 participants on the basis of i) an electrocardiogram showing complete left bundle branch block or atrial flutter/fibrillation or pace-maker rhythm, ii) significant aortic or mitral valve stenosis or regurgitation (more than or equal to moderate), iii) systolic dysfunction, defined as LV ejection fraction < 50%, iv) history of myocardial infarction, heart failure, surgical or percutaneous cardiac revascularization after enrollment. Three hundred and thirteen of the remaining subjects were excluded because of missing echocardiographic or clinical covariates, resulting in a final population of 769 participants. All participants received a detailed description of the study procedures and risks and signed informed participation consent at each study visit.

BMI, calculated as weight (in kilograms) divided by squared height (in meters), was used as the index of general adiposity. WC, defined as the minimal abdominal circumference between the lower edge of the rib cage and the iliac crests, was measured according to a highly standardized procedure and was used as the index of the central adiposity. Brachial blood pressure (BP) was measured in triplicate immediately before echocardiography using an appropriately sized cuff, and the average of 3 systolic and diastolic BP measurements was

used in analyses. Pulse pressure (PP) was computed as $PP = (\text{systolic BP} - \text{diastolic BP})$. Heart rate was recorded before echocardiography from the ECG.

Medications of BLSA participants are recorded at each visit according to the Anatomical Therapeutic Chemical classification system approved by the World Health Organization, and codes related to the cardiovascular system (C codes) were considered for this analysis.

Hypertension was defined as systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mmHg at the time of the echocardiogram, or by the use of antihypertensive medications. Diabetes mellitus was diagnosed according to the 2011 American Diabetes Association criteria or use of diabetes medications. Hypercholesterolemia was defined as total serum cholesterol ≥ 200 mg/dl or by use of lipid-lowering treatment. Current and former smokers were merged into an “ever smoking” category, while a “never smoker” was defined as a person who smoked <100 cigarettes in his or her lifetime. The glomerular filtration rate (GFR), calculated by the simplified modification of diet in renal disease (MDRD) formula, was used to determine renal function, and renal failure was defined as $GFR < 60$ ml/min at the index visit. The participants were identified as obese if their BMI was ≥ 30 Kg/m². Based on the 2004 Adult Treatment Panel III criteria, abdominal obesity was defined as waist circumference >102 cm in men and >88 cm in women.

All echocardiograms were performed by a single diagnostic cardiac sonographer with the same echocardiographic instrument (HP Sonos-5500, Philips, Andover, Massachusetts) following a standardized protocol, and were interpreted by two experienced echocardiographers (S.S.N., J.B.S.). The LV linear dimensions (LV end-diastolic diameter, LV end-systolic diameter) were measured from a parasternal long-axis view according to the guidelines⁹ and were used to determine LV mass, relative wall thickness (RWT), fractional shortening (FS), end-diastolic volume, end-systolic volume and left ventricular ejection fraction (LVEF) as previously described^{10,11}.

Diastolic function was assessed by pulse-wave Doppler examination of mitral inflow (peak E wave, peak A wave, E/A ratio, deceleration time of the E wave, DT) and LV outflow (isovolumetric relaxation time, IVRT). Tissue Doppler systolic (Sm), early (Em) and late (Am) diastolic velocities of the medial and lateral mitral annulus were recorded and averaged, as recommended by the guidelines¹². Left atrial volume (LAV) was measured by planimetry in the apical four-chamber view. All the functional parameters were measured online and offline and in triplicate, and averaged. LAV and LV mass were indexed to body surface area.

Left ventricular diastolic dysfunction was graded on a 4-point ordinal scale, according to the algorithm illustrated in Figure 1 incorporating three different diastolic parameters, including E/A ratio, E/Em ratio and LAV index. The E/A ratio has been used extensively to grade LV diastolic dysfunction and is categorized into one of three mitral inflow patterns, which include normal (E/A between 0.75 and 1.5), impaired LV relaxation (E/A <0.75) and pseudonormal/restrictive LV filling (E/A ≥ 1.5). However, there are subjects with normal diastolic function but E/A ≥ 1.5 that make it difficult to differentiate by mitral inflow velocities alone. Therefore, European and American guidelines recommend a multiparametric evaluation of LV diastolic function^{12,13}, according to the scheme initially proposed by Redfield and colleagues¹⁴. This approach enabled classification of diastolic function into the 4 current categories: normal or grade 0 LV diastolic dysfunction, mild or grade 1 LV diastolic dysfunction (impaired relaxation pattern), moderate or grade 2 LV diastolic dysfunction (pseudonormal LV filling), and severe or grade 3 LV diastolic dysfunction (restrictive LV filling). In our study, the ratio between mitral inflow E velocity and tissue Doppler Em velocity (E/Em ratio) was calculated as an index of LV filling

pressures¹⁵, and an E/Em ratio ≥ 12 was associated with increased LV filling pressures. Since LAV index reflects the cumulative effects of filling pressures over time, LAV index was used instead of E/Em when E/Em ratio was between 8 and 12. According to the guidelines⁹, we used 28 mL/m² as a normal cut off for LAV indexed to body surface area.

All analyses were performed using the SAS package (version 9.2, SAS Institute Inc., Cary, North Carolina). Continuous variables are presented as mean $\pm$ SD and categorical variables are presented as absolute and/or relative frequencies (%). Comparisons between men and women were performed by Student's independent sample t tests for continuous variables. Categorical variables were compared by chi-square tests. Spearman's correlation analyses were performed to determine the association of WC and BMI with continuous parameters of diastolic function in both sexes. Independent association of BMI (Analysis 1 and 4) and WC (Analysis 2 and 5) with LV diastolic dysfunction was determined in the overall sample using binary and multinomial multivariate logistic regression analysis, to assess the risk of LV diastolic dysfunction and specific grades/patterns of LV diastolic dysfunction associated with general and central adiposity, respectively. All models were adjusted for the following covariates: age, gender (only for overall sample analysis), cardiovascular risk factors (including smoking, diabetes, hypertension, hypercholesterolemia, and renal failure), and hemodynamic parameters (heart rate and pulse pressure). To test if central adiposity may explain the relationship between general adiposity and LV diastolic dysfunction, BMI and WC were mutually adjusted in the final models (Analysis 3 and 6). The interaction of WC or BMI with gender was assessed in all the analyses and, when significant, gender-stratified analyses were performed. Difference in mean LV mass index across LV diastolic dysfunction groups was analyzed with ANOVA, and Tukey-Kramer test was used for multiple comparisons among groups. All tests were considered to be significant at the level of $p < 0.05$.

RESULTS

The comparison between men and women with regard to demographic and clinical variables is presented in Table 1. In general, men were significantly older and were more likely to be Caucasians. There was no significant difference between groups for BMI. Mean WC was in the normal range for both genders. Men had higher prevalence of hypertension, diabetes and smoking than women, and the same prevalence of obesity, abdominal obesity, hypercholesterolemia and renal failure. There was no difference in the proportion of subjects taking drugs acting directly on cardiac muscle contraction and relaxation and potentially interfering with our LV diastolic dysfunction estimation (Table 1).

Table 2 compares echocardiographic findings between the two groups. Women had higher E velocities and lower late diastolic and systolic velocities of the mitral annulus. In terms of diastolic function, there were no significant gender differences in the E/A ratio and the E/Em ratio. However, men had a more prolonged IVRT and DT. As expected, women had smaller LAV index, LV end-systolic and end-diastolic diameter, RWT and LV mass index. Systolic function (evaluated by means of FS and LVEF) was comparable between genders. Prevalence of any grade LV diastolic dysfunction was 31% (n=242) in the overall sample. Diastolic dysfunction was present in 29% of women and in 34% of men (p=ns) and the distribution of LV diastolic dysfunction categories was similar in the two groups (Table 2). Since only 7 subjects (4 men and 3 women) displayed LV diastolic dysfunction grade 3 (a restrictive pattern associated with more severe cardiac disease and worse prognosis), they were excluded from the following analyses.

Figure 2 shows the unadjusted correlations and Spearman's correlation coefficients between indexes of adiposity and diastolic function parameters by gender. Associations of WC with

E/A ratio, E/Em ratio and LAV were all significant in both men and women (Figure 2) and the strength of associations was similar between genders. No significant correlation was found between WC and IVRT (women: $r_s = 0.01$, $p = 0.77$; men: $r_s = -0.03$, $p = 0.53$), DT (women: $r_s = 0.11$, $p = 0.11$; men: $r_s = 0.08$, $p = 0.23$) and Em/Am ratio (women: $r_s = -0.06$, $p = 0.23$; men: $r_s = -0.10$, $p = 0.08$).

Among women, E/A ratio, E/Em ratio and LAV were all significantly correlated with BMI, whereas among men only E/Em ratio was significantly correlated with BMI (Figure 2). Correlation of E/A ratio and LAV with BMI in men was in the same direction as in women but the strength of associations was weaker in men and not statistically significant. No significant correlation was found between BMI and IVRT (women: $r_s = -0.02$, $p = 0.75$; men: $r_s = -0.06$, $p = 0.26$), DT (women: $r_s = -0.005$, $p = 0.93$; men: $r_s = -0.03$, $p = 0.69$) and Em/Am ratio (women: $r_s = -0.06$, $p = 0.22$; men: $r_s = -0.10$, $p = 0.06$).

In binary logistic analysis, after adjusting for age, gender, cardiovascular risk factors and hemodynamic parameters, participants with higher BMI and higher WC were more likely to have LV diastolic dysfunction (Table 3, Analysis 1 and 2). A trend for interaction was noted between sex and WC (p for interaction = 0.08, Analysis 2) but not between sex and BMI (p for interaction = 0.47, Analysis 1). In analysis stratified by gender, WC was significantly associated with LV diastolic dysfunction in women but not in men (Table 3, Analysis 2).

BMI and WC were strongly correlated in both genders (women: $r_s = 0.85$, $p < .0001$; men: $r_s = 0.80$, $p < .0001$). When BMI and WC were mutually adjusted in the same model, WC remained significantly associated with the likelihood of LV diastolic dysfunction, whereas the association between BMI and LV diastolic dysfunction was no longer significant (Table 3, Analysis 3). Again, no significant interaction was found between sex and BMI on LV diastolic dysfunction (p for interaction = 0.53), while a trend for interaction was noted between sex and WC (p for interaction = 0.08). In analysis stratified by gender, WC was significantly associated with LV diastolic dysfunction - independently on BMI - in women but not in men (Table 3, Analysis 3).

In multinomial logistic analysis, LV diastolic dysfunction grade 0 and then LV diastolic dysfunction grade 1 were set as the comparison group and BMI and WC were analyzed in separate models and then together. The association of BMI (Analysis 4) and WC (Analysis 5) with LV diastolic dysfunction grade 1 appeared to be similar to their respective association with LV diastolic dysfunction grade 2. When BMI and WC were mutually adjusted in a model, WC displayed about the same small association with LV diastolic dysfunction grade 1 and grade 2 (Table 3, Analysis 6).

In Analysis 6, a borderline statistically significant interaction was found between sex and WC for LV diastolic dysfunction grade 1 (p for interaction = 0.06). We therefore performed an analysis stratified by gender. Similarly to the overall analysis, WC was associated with LV diastolic dysfunction grade 1 and grade 2 only in women, but no significant association was found in men (Table 3, Analysis 6). In these analyses adjusted for WC, BMI was not significantly associated with any specific pattern of LV diastolic dysfunction either in men or in women (Table 3, Analysis 6).

When evaluating differences in structural echocardiographic parameters among the three LV diastolic dysfunction categories, a significant increasing trend was found only for LV mass index and RWT. Average LV mass index was significantly higher with more severe diastolic function in both genders (p for trend = $< .01$, Figure 3). In simple correlation analyses, the associations of BMI and WC with LV mass were significant in both women ($r_s = 0.38$, $p < .0001$; $r_s = 0.29$, $p < .0001$, respectively) and men ($r_s = 0.26$, $p < .0001$; $r_s = 0.29$, $p < .0001$, respectively). When Analysis 3 and Analysis 6 were further adjusted for LV mass

index, the association between WC and LV diastolic dysfunction was substantially unchanged (Analysis 3, OR for WC: 1.04, 95% CI: 1.00 to 1.07, $p=0.03$; Analysis 6, OR for WC, grade 0 to 1: 1.04, 95% CI: 1.00 to 1.09, $p=0.05$; OR for WC, grade 0 to 2: 1.03, 95% CI: 0.99 to 1.08, $p=0.14$).

DISCUSSION

We found that the effect of central adiposity on LV diastolic function was independent of general adiposity and was more pronounced among women than men. These results concur with findings of previous cross-sectional¹⁶ and cohort studies² which have shown a stronger association of WC over BMI for myocardial infarction, ischaemic strokes, and for total and cardiovascular mortality. We propose that a possible pathophysiologic explanation for the association of central adiposity with worsened cardiovascular outcomes is the effect of central adiposity on LV diastolic dysfunction. Visceral adipose tissue is more metabolically active than subcutaneous adipose tissue, and these depots inherently differ in processes involving lipolysis/lipogenesis and in the secretion of adipokines/cytokines, enzymes, hormones and other factors⁷. These differences become so significant at a clinical level that mortality among those with cardiovascular diseases has been shown to be directly associated with central obesity and inversely associated with BMI¹⁷. Confirming WC as a key independent determinant of LV diastolic dysfunction, as done in the current study, may therefore be important in identifying potential areas of future investigations targeting WC specifically to prevent or attenuate the effects of LV diastolic dysfunction on clinically relevant outcomes^{18,19}.

This is the first report in a large study population to address the issue of a different gender-specific impact of central fat accumulation on LV diastolic dysfunction graded by incorporating three different echocardiographic parameters (E/A ratio, E/Em ratio, LAV index). The search for gender-specific associations is both clinically relevant and rooted in the differences in gender body composition. Gender differences in deposition of body fat are evident even at the fetal stage and become more pronounced during puberty²⁰. Women have a more peripheral subcutaneous (“gynoid” or “pear”) distribution of fat in early adulthood but greater parity and the menopause induce a more visceral (“android” or “apple”) distribution of fat with increasing age. Previous studies have demonstrated that increased central adiposity correlates more powerfully with LV diastolic dysfunction than do measures of overall obesity such as BMI, but they did not detect any significant gender difference or interaction between gender and WC on LV diastolic dysfunction^{3,5,6}. Particularly, the limited proportion of male participants recruited in the study from Libhaber et al. (34%) precluded a gender analysis though the authors themselves affirmed that the effect of WC on several diastolic parameters they reported might be restricted to women³. Similarly, Tsioufis et al. noted that the adverse effect of abdominal obesity on several continuous echocardiographic diastolic parameters was more pronounced among hypertensive females than males, and WC turned out to be a major determinant of LV mass only in women⁴. The current study expands on these prior studies by demonstrating that after accounting for the association of BMI with LV diastolic dysfunction, WC is still independently associated with LV diastolic dysfunction. In addition, we demonstrated that the association between WC and LV diastolic dysfunction is tendentially stronger in women than in men compared to previous studies. Compared to previous studies^{3–6}, our sample was relatively older, included a discrete component of non-white subjects (especially among women) and had a lower prevalence of obesity with comparable mean WC. Since there are significant age and ethnic differences in body composition²¹, our results may, in part, be explained by the age, the racial characteristics, and the particular body fat distribution of our female sample.

Apart from the gender differences in body composition, there are several other possible mechanisms that may explain the association of WC with LV diastolic dysfunction. We confirmed a positive significant association between LV mass index, anthropometric measures of adiposity and worsening diastolic function in both genders (Figure 3). The association between WC and LV diastolic dysfunction, however, was only slightly weakened after further adjusting our models for LV mass index, suggesting that different mechanisms other than LV hypertrophy may link the increase in WC to the impairment in LV diastolic function, which serves to further highlight the independent clinical relevance of central adiposity. Visceral fat content correlates with triglyceride cell content and lipid accumulation in many tissues, including the myocardium, and has been independently associated with impaired LV relaxation²². Some evidences suggest that changes in myocardial lipid content may also lead to LV diastolic dysfunction by increasing susceptibility to cardiac lipotoxicity and altering myocardial calcium homeostasis²³. At a population level, LV mass and geometry may therefore have little or no role to play in the pathogenesis of obesity-induced LV diastolic dysfunction³, and LV mass would increase just because the impact of other risk factors such as hypertension on the left ventricle is enhanced by visceral adiposity²⁴. Further prospective studies are required to assess this hypothesis and clarify the mechanisms that connect abdominal fat accumulation with diastolic abnormalities without LV hypertrophy.

As previously demonstrated³, the present study confirms negative correlation between indexes of adiposity and E/A ratio (Figure 2). However, E/A ratio alone does not adequately discriminate subjects with normal or abnormal diastolic function, since high E/A ratio values are commonly found both in healthy normal people or as a “psuedonormal” pattern in patients with advanced cardiac dysfunction. Furthermore, the prognostic role presently attributed to elevated E/A ratio remains controversial²⁵. Mitral valve inflow velocities are also significantly influenced by increase in preload, a condition frequently encountered in obese subjects. The diastolic classification in the present study attempted to circumvent these issues by combining both structural and dynamic echocardiographic parameters according to the recommendations of the American Society of Echocardiography¹². However, our current analysis suggests that this classification does not help to evaluate the effect of body composition on LV diastolic dysfunction in detail, because the true difference we found occurred only between LV diastolic dysfunction grade 0 (absence of LV diastolic dysfunction) and all the other grades together (binary regression). When we tried to estimate the association of WC with a specific pattern of LV diastolic dysfunction (multinomial regression), we did not detect any differences in the impact of central adiposity on different grades/patterns of LV diastolic dysfunction (see Table 3, Analyses 5 and 6). Since our results and those of a previous study³ have shown an important inverse correlation between WC and E/A ratio, we would expect the association between WC and LV diastolic dysfunction grade 1 to be significantly stronger than that with LV diastolic dysfunction grade 2. A continuous integrated parameter (or score) to assess diastolic dysfunction, rather than diastolic grade, may therefore better describe the progression and severity of LV diastolic dysfunction and address this question.

Finally, there is an emerging interest in the relationship between asymptomatic LV diastolic dysfunction and heart failure with preserved ejection fraction (HFpEF), particularly since recent studies have confirmed the role of asymptomatic LV diastolic dysfunction in the eventual development of HFpEF^{18,19}. Incident HFpEF is increased in obese individuals²⁶, and obesity is an independent risk factor for the development of HFpEF²⁷. For reasons that are not completely understood, obese and overweight women are at higher risk than obese and overweight men for developing HFpEF²⁶. Recently, two prospective studies^{28,29} demonstrate an independent association between WC and incident heart failure. The current study supports the link between WC and HFpEF through the relationship of central obesity

on prevalence and development of LV diastolic dysfunction. Since there is no specific evidence based treatment to attenuate LV diastolic dysfunction or HFpEF, identifying markers for the development of LV diastolic dysfunction, as in the present study, may be clinically relevant with respect to eventual prevention or treatment of HFpEF. Additionally, since specific treatments have yet to be identified for HFpEF, the current study suggests the potential role for targeting reduction of WC as treatment for HFpEF.

The limitations of the study were first the cross-sectional, instead of prospective, nature of the study design. Second, because the mean age of the study cohort was high, as was the prevalence of cardiovascular risk factors, our results may not be directly extrapolated to younger populations with lower cardiovascular risk profiles. Third, we cannot exclude the influence of CV medications, though they have been taken into account to estimate the prevalence of hypertension and hypercholesterolemia, which were adjusted for in our models. Fourth, where ordinal logistic regression was previously used to assess predictors of increased LV diastolic dysfunction severity^{19,30}, proportional odds assumption was tested using Score Test and was invalid, preventing us from performing this further analysis. Fifth, we did not find an association of BMI or WC with a specific pattern of LV diastolic dysfunction; this could also be due to the small number of participants with LV diastolic dysfunction grade 2. Finally, the high degree of correlation between BMI and WC in this population introduced the problem of collinearity. Collinearity inflates the estimates of variance in both the continuous and categorical analyses when BMI and WC are entered together into the regression models. However, since we found similar correlation coefficients between BMI and WC in men and women (0.80 and 0.85, respectively) and variance inflation factor values for BMI and WC were within acceptable limits (< 5), we believe our conclusion of the relative importance of WC still applies.

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Figure 1. Criteria for Classification of Diastolic Function
See text for abbreviations and comments.

Figure 2. Relation between anthropometric measures and echocardiographic diastolic parameters

Scatter plots with regression lines by gender show the relation of waist circumference (left side) and body mass index (right side) and continuous functions diastolic parameters, including E/A ratio (upper panel), E/Em ratio (middle panel) and left atrial volume, LAV (lower panel). See text for comments.

Figure 3. LV mass index and diastolic dysfunction severity

The two box plots show the relationship between left ventricular (LV) mass index and diastolic dysfunction (DD) grade in women and men. In both genders, increasing LV mass index is associated with more impaired diastolic function.

Table 1

Demographic and Clinical Characteristics of the Study Cohort.

	Overall (n = 769)	Men (n = 370)	Women (n = 399)
Age (yrs)	64 ± 13	66 ± 13	62 ± 13 [†]
Race			
White	64%	71%	59% [‡]
Black	29%	24%	33% [‡]
Other	7%	5%	8%
Body mass index (kg/m ²)	27 ± 5	27 ± 4	27 ± 5
Waist circumference (cm)	92 ± 12	99 ± 10	85 ± 11 *
Systolic blood pressure (mmHg)	120 ± 17	124 ± 15	117 ± 17 *
Diastolic blood pressure (mmHg)	67 ± 9	70 ± 8	65 ± 9 *
Pulse pressure (mmHg)	53 ± 13	54 ± 13	52 ± 14
Heart rate (beats/min)	66 ± 11	65 ± 11	67 ± 10 [†]
Total cholesterol (mg/dl)	193 ± 36	186 ± 35	199 ± 36 *
Glomerular filtration rate (ml/min)	78 ± 17	78 ± 17	77 ± 17
Smoker (ever)	47%	56%	38% *
Diabetes mellitus	11%	16%	7% [†]
Obesity	23%	23%	23%
Abdominal obesity	34%	34%	35%
Hypertension	45%	52%	39% [†]
Hypercholesterolemia	49%	52%	47%
Renal failure	11%	9%	13%
Medications, ATC code			
Cardiac therapy, C01	13%	11%	14%
Diuretics, C03	14%	14%	14%
Beta Blocking Agents, C07	15%	17%	12%
Calcium channel blockers, C08	10%	11%	9%
Renin-angiotensin system, C09	24%	28%	19% [‡]
Lipid modifying, C10	38%	42%	34% [‡]

* p< 0.0001.

[†] p< 0.001.[‡] p< 0.01 compared with men. Obesity was defined as a body mass index ≥ 30.

Abdominal obesity was defined as waist circumference>102 cm in men and >88 cm in women. See methods section for other definitions.

Table 2

Echocardiographic Characteristics of the Study Cohort.

	Overall (n = 769)	Men (n = 370)	Women (n = 399)
Early transmitral velocity (E, cm/s)	76.7 ± 17.3	71.8 ± 16.5	79.2 ± 17.3 *
Late transmitral velocity (A, cm/s)	77.0 ± 18.5	75.3 ± 18	78.4 ± 18.8
E/A ratio	1.0 ± 0.4	1.0 ± 0.4	1.1 ± 0.3
Systolic mitral annulus velocity (Sm, cm/s)	8.4 ± 1.6	8.7 ± 1.7	8.2 ± 1.5 *
Early diastolic mitral annulus velocity (Em, cm/s)	9.7 ± 2.4	9.5 ± 2.4	9.9 ± 2.4
Late diastolic mitral annulus velocity (Am, cm/s)	9.8 ± 2.1	10.2 ± 2.1	9.4 ± 2.1 *
E/Em ratio	8.2 ± 2.4	8.0 ± 2.3	8.4 ± 2.6
Em/Am ratio	1.3 ± 0.5	1.4 ± 0.5	1.2 ± 0.4 *
Isovolumetric relaxation time (ms)	80 ± 19	82 ± 22	79 ± 16 ‡
Deceleration time (ms)	225 ± 52	233 ± 54	217 ± 48 †
Left atrial volume indexed to body surface area (ml/m ²)	21 ± 13	23 ± 15	19 ± 11 †
Left ventricular end-diastolic diameter (mm)	44 ± 1	46 ± 6	43 ± 5 *
Left ventricular end-systolic diameter (mm)	28 ± 1	29 ± 5	27 ± 4 *
Relative wall thickness	0.44 ± 0.1	0.5 ± 0.1	0.4 ± 0.1 *
Fractional shortening (%)	37 ± 8	36 ± 7	37 ± 8
Left ventricular end-diastolic volume (ml)	91 ± 27	99 ± 29	83 ± 22 *
Left ventricular ejection fraction (%)	66 ± 10	65 ± 10	67 ± 10
Left ventricular mass indexed to body surface area (g/m ²)	76.8 ± 25.6	84.8 ± 27.2	69.3 ± 21.6 *
Diastolic function categories			
Grade 0, normal	527 (69%)	243 (66%)	284 (71%)
Grade 1, mild	147 (19%)	81 (22%)	66 (17%)
Grade 2, moderate	88 (11%)	42 (11%)	46 (11%)
Grade 3, severe	7 (1%)	4 (1%)	3 (1%)

*
p < 0.0001.†
p < 0.001.‡
p < 0.01 compared with men.

Table 3

Association of left ventricular diastolic dysfunction with body mass index and waist circumference.

Relation between body mass index and waist circumference with left ventricular diastolic dysfunction *									
Overall			Women			Men			
O.R.	95% C.I.	P	O.R.	95% C.I.	P	O.R.	95% C.I.	P	
Analysis 1									
BMI	1.07 (1.03–1.12)	<.001	1.09 (1.04–1.15)	<.001	1.06 (0.99–1.13)	0.10			
Analysis 2									
WC	1.04 (1.02–1.06)	<.0001	1.06 (1.03–1.09)	<.0001	1.02 (0.99–1.05)	0.12			
Analysis 3									
WC	1.04 (1.01–1.08)	0.02	1.08 (1.04–1.14)	<.001	1.00 (0.95–1.05)	0.91			
BMI	1.00 (0.93–1.07)	0.98	0.95 (0.86–1.04)	0.27	1.06 (0.94–1.20)	0.33			
Relation between body mass index and waist circumference with different grades of left ventricular diastolic dysfunction *									
Overall			Women			Men			
O.R.	95% C.I.	P	O.R.	95% C.I.	P	O.R.	95% C.I.	P	
Analysis 4									
BMI, grade 0 to 1	1.09 (1.04–1.14)	<.001	1.11 (1.04–1.17)	<.001	1.06 (0.98–1.15)	0.12			
BMI, grade 0 to 2	1.07 (1.01–1.13)	0.02	1.08 (1.01–1.15)	0.03	1.06 (0.96–1.17)	0.23			
BMI, grade 1 to 2	0.98 (0.92–1.04)	0.56	0.97 (0.90–1.05)	0.52	1.00 (0.90–1.11)	0.97			
Analysis 5									
WC, grade 0 to 1	1.04 (1.02–1.07)	<.001	1.07 (1.04–1.10)	<.0001	1.02 (0.99–1.06)	0.23			
WC, grade 0 to 2	1.03 (1.01–1.06)	<.01	1.05 (1.02–1.09)	<.01	1.03 (0.99–1.08)	0.12			
WC, grade 1 to 2	0.99 (0.96–1.02)	0.46	0.98 (0.95–1.02)	0.45	1.01 (0.97–1.06)	0.61			
Analysis 6									
WC, grade 0 to 1	1.04 (1.00–1.08)	0.04	1.09 (1.03–1.16)	<.01	0.99 (0.93–1.05)	0.74			
BMI, grade 0 to 1	1.01 (0.93–1.10)	0.83	0.94 (0.84–1.06)	0.31	1.09 (0.95–1.25)	0.21			
WC, grade 0 to 2	1.04 (0.99–1.09)	0.06	1.07 (1.01–1.14)	0.02	1.03 (0.96–1.10)	0.47			

Relation between body mass index and waist circumference with different grades of left ventricular diastolic dysfunction *									
	Overall			Women			Men		
	O.R.	95% C.I.	P	O.R.	95% C.I.	P	O.R.	95% C.I.	P
BMI, grade 0 to 2	0.99	(0.90–1.09)	0.85	0.95	(0.84–1.08)	0.47	1.03	(0.86–1.21)	0.83
WC, grade 1 to 2	1.00	(0.95–1.05)	0.95	0.98	(0.91–1.05)	0.57	1.04	(0.96–1.12)	0.37
BMI, grade 1 to 2	0.98	(0.88–1.10)	0.74	1.01	(0.88–1.17)	0.87	0.93	(0.77–1.13)	0.47

* All models areadjusted for age, gender, smoking, diabetes, hypertension, hypercholesterolemia, renal failure, heart rate, pulse pressure.
O.R. = odds ratio; C.I.= confidence interval.