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ORIGINAL RESEARCH

Measures of Left Ventricular Diastolic Function and Cardiorespiratory Fitness According to Glucose Metabolism Status: The Maastricht Study

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BACKGROUND: This cross-sectional study evaluated associations between structural and functional measures of left ventricular diastolic function and cardiorespiratory fitness (CRF) in a well-characterized population-based cohort stratified according to glucose metabolism status.

METHODS AND RESULTS: Six hundred seventy-two participants from The Maastricht Study (mean±SD age, 61±9 years; 17.4% prediabetes and 25.4% type 2 diabetes mellitus) underwent both echocardiography to determine left atrial volume index, left ventricular mass index, maximum tricuspid flow regurgitation, average e′ and E/e′ ratio; and submaximal cycle ergometer test to determine CRF as maximum power output per kilogram body mass. Associations were examined with linear regression adjusted for cardiovascular risk and lifestyle factors, and interaction terms. After adjustment, in normal glucose metabolism but not (pre)diabetes, higher left atrial volume index (per 1 mL/m^2), left ventricular mass index (per 1 g/m$^{2.7}$), maximum tricuspid regurgitation flow (per 1 m/s) were associated with higher CRF (maximum power output per kilogram body mass; β in normal glucose metabolism 0.015 [0.008–0.023], $P_{interaction}$ (pre)diabetes <0.10; 0.007 [−0.001 to 0.015], $P_{interaction}$ type 2 diabetes mellitus <0.10; 0.129 [0.011–0.246], $P_{interaction}$ >0.10; for left atrial volume index, left ventricular mass index, maximum tricuspid regurgitation flow, respectively). Furthermore, after adjustment, in all individuals, higher average E/e′ ratio (per unit), but not average e′, was associated with lower CRF (normal glucose metabolism −0.044 [−0.071 to −0.016]), $P_{interaction}$ >0.10).

CONCLUSIONS: In this population-based study, structural and functional measures of left ventricular diastolic function were independently differentially associated with CRF over the strata of glucose metabolism status. This suggests that deteriorating left ventricular diastolic function, although of small effect, may contribute to the pathophysiological process of impaired CRF in the general population. Moreover, the differential effects in these structural measures may be the consequence of cardiac structural adaptation to effectively increase CRF in normal glucose metabolism, which is absent in (pre)diabetes.

Key Words: cardiorespiratory fitness ■ left ventricular diastolic dysfunction ■ physical fitness ■ population-based ■ prediabetes ■ type 2 diabetes mellitus

Left ventricular (LV) diastolic function is an important determinant of cardiorespiratory fitness (CRF) in individuals with established cardiovascular disease (CVD) or CVD risk factors.[1,2] The latter may be especially so for individuals with type 2 diabetes mellitus (T2D) because of the existence of a hyperglycemia-driven diabetic cardiomyopathy.[3] LV diastolic function may be particularly negatively influenced by T2D and

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CLINICAL PERSPECTIVE

What Is New?

- In this population-based study, structural and functional measures of left ventricular diastolic function were independently differentially associated with cardiorespiratory fitness over a strata of glucose metabolism status that suggests that deteriorating left ventricular diastolic function may contribute to the pathophysiological process of impaired cardiorespiratory fitness in the general population.
- In addition, structural adaptations of the left atrium and left ventricle may be different in (pre)diabetes as compared with normal glucose metabolism, indicating an absence of physiological cardiac structural adaptation in (pre)diabetes possibly explained by a diabetic cardiomyopathy.

What Are the Clinical Implications?

- Our findings emphasize the need for future prospective studies that examine the usefulness of left ventricular diastolic function as potential targets in preventive and therapeutic strategies for impaired cardiorespiratory fitness in the general population and in (pre)diabetes, and the exact cardiovascular mechanisms to better understand the cardiac adaptation process in (pre)diabetes (eg, mechanisms of diabetic cardiomyopathy) in the early development of diastolic dysfunction.

Nonstandard Abbreviations and Acronyms

CRF	cardiorespiratory fitness
GMS	glucose metabolism status
LAVI	left atrial volume index
LVMI	left ventricular mass index
NGM	normal glucose metabolism
T2D	type 2 diabetes mellitus
W_{max}	estimated maximum power output

thus its association with CRF, because of synergy between diabetic cardiomyopathy and other CVD risk factors.[4] However, the concept of diabetic cardiomyopathy is under debate,[5] and it is currently unclear whether this concept also is present in individuals with prediabetes.[6]

To what extent the link between LV diastolic function and CRF expands to the general population at large, including individuals with a is less clear.[7–13] Population-based data focusing solely on the association between LV diastolic function and CRF in individuals with (pre)diabetes do not exist. Population-based studies on the association between LV diastolic function and CRF[7–13] in the general population are heterogeneous in their results. Moreover, these studies were relatively small,[7,8,10–13] included only a limited number of individuals with prediabetes,[9,12,13] and/or did not adequately adjust for (multiple) confounders (Table S1).[7,8,11,12] Furthermore, the pathophysiology of LV diastolic function is complex and may give inhomogeneous responses because of the interplay between different compensatory mechanisms.[14] For instance, unfavorable alterations in LV myocardial relaxation may be compensated for by an increased atrial contribution to the LV filling (at higher filling pressures) without any pathological changes in LV or left atrial volume.[15–17]

In view of these considerations, the aim of the present study was to evaluate (1) the associations between structural and functional measures of LV diastolic function[14] and CRF, measured as estimated maximum power output adjusted for body mass (W_{max} per kilogram), in a well-characterized population-based cohort stratified according to glucose metabolism status (GMS); and (2) whether these associations differed between individuals with normal glucose metabolism (NGM) and (pre)diabetes.

METHODS

Study Population and Design

We used data from The Maastricht Study, an observational prospective population-based cohort study. The rationale and methodology have been described previously.[18] In brief, the study focuses on the cause, pathophysiology, complications, and comorbidities of T2D and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged between 40 and 75 years living in the southern part of the Netherlands. Participants were recruited through mass media campaigns as well as from the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2D status, with an oversampling of individuals with T2D, for reasons of efficiency. Eight hundred sixty-six participants, who completed the baseline survey between November 2010 and March 2012, were included. To augment statistical power, another random sample of 218 participants was added who had completed the baseline survey between April 2012 and April 2013 (following the same recruitment strategy). The examinations of each participant were performed within a time window of 3 months. The study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Minister of Health, Welfare and Sports of

the Netherlands (Permit 131088-105234-PG) and follows the Declaration of Helsinki. All participants gave written informed consent. The present study was reported as per the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for observational cohort studies. Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to The Maastricht Study Management Team at research.dms@mumc.nl.

From the 1084 individuals in this extended sample of the study population, echocardiography was obtained in 933 individuals. Individuals were excluded on the basis of exclusion criteria (N=7), missing data on CRF (N=154), missing data on covariates (N=62), and missing data on 2-dimensional echocardiography variables (N=38) or tissue Doppler imaging data (N=71). This resulted in 672 (2-dimensional echocardiography study population) and 639 (tissue Doppler imaging echocardiography study population) individuals eligible for the current analyses (Figure S1).

Echocardiography: Measures of LV Diastolic Function

Echocardiograms were obtained according to a standardized protocol consisting of 2-dimensional, M-mode, color flow Doppler, pulsed and continuous wave Doppler, and tissue Doppler recordings with use of standard echo equipment (Vivid E9 with 2.5–3.5 MHz and 4 V transducer; GE Vingmed). All recordings were digitally stored and analyzed off-line (EchoPAC PC, version 112; GE Healthcare) by 4 researchers blinded to GMS and other covariates.

LV diastolic function was assessed according to the 2016 guidelines with the use of both structural and functional echocardiographic variables, namely left atrial volume index (LAVI), LV mass index (LVMI), average E/e′ ratio, average e′, and maximum tricuspid regurgitation flow.[14] Higher values of these measures apart from average e′ indicate deteriorating LV diastolic function in patients with heart failure, which already may be seen in the general population.[1,14] Biplane end-systolic left atrial volume was measured and indexed to body surface area. LV mass was calculated with the use of end-diastolic LV diameter, interventricular septum diameter, and end-diastolic LV posterior wall thickness, and indexed by height$^{2.7}$. Maximal tricuspid valve regurgitation velocity was measured with continuous wave Doppler recordings. Average E/e′ ratio was calculated from the mitral peak flow velocity of the filling wave during early inflow (E) obtained with pulsed-wave Doppler and the septal and lateral early (e′) diastolic longitudinal velocity obtained with pulsed Doppler tissue echocardiography. Further details on echocardiographic procedures and variables including reproducibility are provided in Data S1.

Submaximal Cycle Ergometer Test: CRF

The submaximal cycle ergometer test to determine CRF in W_{max} was performed as described previously.[19] As an objective measure of CRF, estimated W_{max} per kilogram was used.[20,21] W_{max} was estimated from a graded submaximal exercise protocol performed on a cycle ergometer system (CASETM version 6.6 in combination with e-bike; GE Healthcare, Milwaukee, WI). Exclusion criteria for the submaximal cycle ergometer test were: having suffered from CVD 3 months before the ergometer test, having a resting ECG with previously unknown abnormalities, having severe hypertension (systolic blood pressure ≥180 and/or diastolic blood pressure ≥110), or being in the possession of an implantable cardioverter-defibrillator/pacemaker. Further details on the protocol and estimation of W_{max} are provided in Data S1.

Covariates

We assessed glucose metabolism, clinical characteristics of patients, lipid profile, markers of renal function, educational level, and self-reported physical activity as described previously.[18,19,22,23] Further details on the covariates are provided in Data S1.

Statistical Analysis

Descriptive statistics are presented as mean±standard deviation, median (interquartile range), or frequency (percentage), as appropriate; all variables were checked for the assumption of normality). Comparisons of population characteristics between groups were made by use of ANOVA for continuous variables, log-transformed if necessary, or by χ^2 test for dichotomous or categorical variables.

Associations between structural and functional measures of LV diastolic function and CRF were investigated with multivariable linear regression analyses in the study population stratified according to GMS. The analyses were adjusted for sex, age, and height (Model 1), and additionally adjusted for prior CVD, smoking status, total cholesterol/high-density lipoprotein ratio, triglycerides, use of lipid-modifying medication, office systolic pressure, use of antihypertensive medication, estimated glomerular filtration rate, albuminuria, health status, and alcohol use (Model 2). Because of its role as a possible mediator or ascending proxy, waist was added in a separate model (Model 3), because a model including waist might be at risk of overadjustment.[24] In addition, we investigated whether or not these associations differed among individuals with different GMS by adding interaction terms in Model 2.

Furthermore, we conducted several additional analyses to test the robustness of our results. First, we repeated the analyses with diastolic function according to 2016 guidelines as categorical determinant,[14] and in the total study population. Second, we replaced LAVI with nonindexed left atrial volume, and LVMI indexed by height with LVMI indexed by body surface area, or by LV mass, to test the influence of the index used. Third, we replaced CRF as W_{max} per kilogram by CRF as the percentage of the predicted W_{max} to put the results in a clinical perspective.[25] Fourth, we additionally adjusted Model 2 for moderate-to-vigorous physical activity.[26] Fifth, to restrict the analyses to subclinical disease, we repeated the analyses excluding individuals with prior coronary heart disease, current atrial fibrillation or flutter, wall motion abnormalities, significant valvular dysfunction, or functional mobility limitations. Sixth, the analyses were repeated with the replacement of office systolic pressure in Model 2 by office diastolic pressure,[27] their 24-hour equivalents,[28] the presence of hypertension, and with additional adjustment for renin-angiotensin system inhibitors or β-blockers. Seventh, we replaced waist in Model 3 by body mass index or weight. Last, we used interaction terms added to Model 2, additionally adjusted for the interaction between measures of LV diastolic function and GMS, to examine whether the investigated associations were modified by sex.

All statistical analyses were performed using IBM SPSS Statistics version 23 (IBM, Armonk, NY). A 2-sided $P<0.05$ was considered statistically significant, except for interaction terms, where a $P<0.10$ was used. Multicollinearity was assessed by collinearity diagnostics (ie, tolerance <0.2 and/or variance inflation factor >10). Because of the observational nature of our study, we made no corrections for multiple comparisons in our analyses.[29]

RESULTS

Characteristics of the Study Population

The study population with a mean±SD age of 61±9 years consisted of 366 (57.3%), 111 (17.4%), and 162 (25.4%) individuals with NGM, prediabetes, and T2D, (pre)diabetes were older, more often men, had higher body mass index, lower high-density lipoprotein, higher triglycerides, lower estimated glomerular filtration rate, and less physical activity. In addition, they more often suffered from prior CVD, hypertension, albuminuria, and mobility limitations, and more frequently used antihypertensive and lipid-modifying medication (Table 1).

General characteristics of the tissue Doppler imaging echocardiography study population stratified according to GMS and according to tertiles of average E/e′ ratio are given in Tables 1 and 2 and Tables S2 and S3, respectively. Individuals with (pre)diabetes had higher average E/e′ ratio and higher LVMI indicating deteriorating LV diastolic function, more frequent abnormal diastolic function grade, and lower CRF (Tables 1 and 2). The study population in which 2-dimensional echocardiography was available (NGM N=380 [56.5%], prediabetes N=115 [17.1%], and T2D N=177 [26.3%]) overlapped for 94% with the tissue Doppler imaging study population and was comparable with regard to age, sex, and cardiometabolic risk factors (Figure S1 and Table S4).

Individuals in the middle and highest tertile of the average E/e′ ratio, as compared with the lowest tertile, were older, had higher body mass index, lower high-density lipoprotein, higher triglycerides, and lower estimated glomerular filtration rate. In addition, they more often had T2D, prior CVD, hypertension, and albuminuria, more frequently used antihypertensive and lipid-modifying medication, and had a lower CRF (Table S1).

Individuals with missing values were older, more often had T2D, had a worse cardiovascular risk profile, were less physically active, had higher average E/e′ ratio and lower CRF. Within the strata of GMS, similar patterns were seen, although to a lesser extent, and somewhat more pronounced in individuals with T2D (Tables S4 and S5).

Associations Between Measures of LV Diastolic Function and CRF

Table 3 and the Figure show the associations between measures of LV diastolic function and CRF in W_{max} per kilogram in individuals with NGM, prediabetes, and T2D.

Structural Measures of LV Diastolic Function

After adjustment for potential confounders (Model 2), higher LAVI (per 1 mL/m^2) was, in NGM, significantly associated with higher CRF (regression coefficient for LAVI beta [95% CI] 0.015; [0.008–0.023]). In prediabetes and T2D, no significant associations were observed between LAVI and CRF (–0.003 [–0.017 to 0.011] and 0.000 [–0.009 to 0.010], respectively). This association did differ significantly in individuals with prediabetes and T2D as compared with NGM ($P_{interaction}$ between prediabetes and T2D, and LAVI were 0.038 and 0.066, respectively; Table S6).

After adjustment for potential confounders, higher LVMI (per 1 g/m$^{2.7}$) was, in NGM, borderline significantly associated with higher CRF (0.007 [–0.001 to 0.015]). In prediabetes and T2D, no significant associations were observed between LVMI and CRF (–0.004 [–0.017 to 0.009]) and –0.006 [–0.016 to 0.004]), respectively). These associations did significantly differ in individuals

Table 1. General Characteristics of the Tissue Doppler Imaging Echocardiography Study Population According to Glucose Metabolism Status

	Normal Glucose Metabolism, n=366	Prediabetes, n=111	Type 2 Diabetes Mellitus, n=162	*P* Value
Demographics				
Men, n (%)	43	61	70	<0.001
Age, y	60±8	62±7	63±7	<0.001
Educational level, low/middle/high, %	10.7/39.2/50.1	17.1/44.1/38.7	25.9/43.2/30.9	<0.001
Prior cardiovascular disease, %	10	13	19	0.004
Prior coronary heart disease, %	3	6	9	0.005
Current atrial fibrillation or flutter, %*	0.0	0.0	1.3	0.030
Blood pressure				
Office systolic pressure, mm Hg	130±16	139±16	145±17	<0.001
Office diastolic pressure, mm Hg	75±10	79±10	78±10	<0.001
24-hour systolic pressure, mm Hg†	116±11	121±12	122±11	<0.001
24-hour diastolic pressure, mm Hg†	74±7	74±8	73±7	0.929
Hypertension, %	36	60	79	<0.001
Metabolic variables				
BMI, kg/m^2	25.3±3.3	27.5±3.4	28.6±3.4	<0.001
Waist, cm	90.4±10.5	98.2±10.6	102.7±10.1	<0.001
Total cholesterol, mmol/L	5.59±0.99	5.46±1.09	4.49±0.92	<0.001
HDL, mmol/L	1.54±0.49	1.38±0.36	1.19±0.32	<0.001
LDL, mmol/L	3.54±0.87	3.39±0.99	2.53±0.78	<0.001
Triglycerides, mmol/L	1.01 [0.75–1.40]	1.27 [0.88–1.78]	1.63 [1.16–2.08]	<0.001
Total-to-HDL-cholesterol ratio	3.95±1.31	4.17±1.18	3.93±0.94	0.891
HbA1C, in %‡	5.5±0.3	5.8±0.4	6.7±0.9	<0.001
Fasting plasma glucose, mmol/L	5.2±0.4	6.0±0.5	7.6±1.7	<0.001
Kidney function				
eGFR, mL/min per 1.73 m^2	91.0±13.7	85.1±14.6	86.4±16.2	<0.001
Albuminuria, %	3.3	4.5	17.3	<0.001
Lifestyle variables				
Smoking status: never/former/current, %	38.9/45.5/15.6	28.8/61.3/9.9	27.8/57.4/14.8	0.101
Alcohol use: no/low/high, %	13.2/56.2/30.7	14.4/52.3/33.3	26.5/48.1/25.3	0.006
Moderate to vigorous physical activity, h/wk§	5.5 [3.0–9.0]	4.5 [2.7–7.1]	3.6 [2.3–10.0]	<0.001
Medication				
Antihypertensive medication, %	20	40	63	<0.001
RAS inhibitors, %	13	30	51	<0.001
β-blockers, %	6	19	33	<0.001
Diuretics, %	6	16	19	<0.001

(*Continued*)

Table 1. Continued

	Normal Glucose Metabolism, n=366	Prediabetes, n=111	Type 2 Diabetes Mellitus, n=162	*P* Value
Calcium antagonists, %	3	6	13	<0.001
Oral antidiabetics and/or insulin use	…	…	74	…
Lipid-modifying medication, %	14	36	75	<0.001
Cardiorespiratory fitness, W_{max}	168.9±48.6	168.8±46.1	158.1±42.7	0.023
Cardiorespiratory fitness adjusted for body mass, W_{max}/kg	2.28±0.55	2.08±0.48	1.89±0.49	<0.001
Predicted cardiorespiratory fitness, predicted W_{max}	149.2±49.5	153.5±54.8	158.4±47.9	0.145
Cardiorespiratory fitness, % of predicted W_{max}	118.8±29.2	120.7±43.1	106.7±31.2	<0.001
Mobility limitation, %‖	12	26	30	<0.001

Data are presented as mean±SD, median [interquartile-range], or frequency (%) as appropriate. Data present the tissue Doppler imaging echocardiography population for regression Models 1 to 3. Linear trend was tested with ANOVA or χ^2 test as appropriate. BMI indicates body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NGM, normal glucose metabolism; RAS, renin angiotensin system; T2D, type 2 diabetes mellitus; and W_{max}, estimated maximum power output.

Numbers for specific variables (total, NGM/prediabetes/T2D) are:

*Current atrial fibrillation or flutter 610, 350/103/157.

†24-hour blood pressure measurements 590, 340/101/149.

‡HbA1c 637, 365/110/162.

§Moderate to vigorous physical activity 554, 322/94/138.

‖Mobility limitation 636, 364/110/162.

with T2D, but not prediabetes, as compared with NGM ($P_{interaction}$ between prediabetes and T2D and LVMI were 0.318 and 0.058, respectively; Table S6).

After further adjustment for waist (Model 3), in NGM, the association between LAVI and CRF was not materially altered, whereas the association between LVMI and CRF was further strengthened.

Functional Measures of LV Diastolic Function

After adjustment for potential confounders (Model 2), higher average E/e′ ratio (per unit) was associated with lower CRF. In NGM (–0.044 [–0.071 to –0.016]) and T2D (–0.033 [–0.064 to –0.001]), the association was statistically significant, but in prediabetes it was not (–0.030 [–0.072 to 0.012]). The associations did not significantly differ in prediabetes and T2D as compared with NGM ($P_{interaction}$ >0.10; Table S6).

In addition, after adjustment for potential confounders (Model 2), higher average e′ (per centimeter per second) was not significantly associated with CRF in all 3 groups of metabolism status (NGM 0.013 [–0.016 to 0.042], prediabetes 0.040 [–0.016 to 0.095], T2D –0.010 [–0.057 to 0.037]). Analyses after adjustment for age, sex, and height show similar results as with average E/e′ ratio (Table 3). The associations did not significantly differ in prediabetes and T2D as compared with NGM ($P_{interaction}$ >0.10; Table S6). In contrast, after adjustment for potential confounders, higher maximum tricuspid regurgitation flow (per 1 m/s) was, in NGM, significantly associated with higher CRF (0.129 [0.011–0.246]). In prediabetes and T2D, no significant associations were observed between maximum tricuspid flow and CRF (–0.030 [–0.207 to 0.146] and –0.053 [–0.193 to 0.087], respectively). These associations did not significantly differ in prediabetes and T2D as compared with NGM ($P_{interaction}$ >0.10; Table S6).

These associations were at most slightly attenuated after further adjustment for waist (Model 3).

Additional Analysis

After adjustment for potential confounders (Model 2), abnormal as compared with normal diastolic function according to 2016 guidelines was, in NGM, borderline significantly associated with higher CRF (0.165 [–0.004;0.335]). In prediabetes and T2D, no significant associations were observed between abnormal as compared with normal diastolic function (–0.053 [–0.329 to 0.224] and –0.065 [–0.301 to 0.170], respectively; Table 3). Indeterminate diastolic function as compared with normal diastolic function was, in NGM, prediabetes, and T2D, not associated with CRF (0.050 [–0.079 to 0.146] and –0.158 [–0.369 to 0.052], and –0.115 [–0.302 to 0.073], respectively; Table 3). These associations did not significantly differ in prediabetes and T2D as compared with NGM ($P_{interaction}$ >0.10; Table S6).

Table 2. Echocardiographic Characteristics of the Tissue Doppler Imaging Echocardiography Study Population According to Glucose Metabolism Status

	Normal Glucose Metabolism, n=366	Prediabetes, n=111	Type 2 Diabetes Mellitus, n=162	*P* Value
Measures LV diastolic function				
Average E/e′ ratio	7.6±1.9	8.6±2.4	8.9±2.3	<0.001
Average e′, cm/s	9.5±2.2	8.2±2.0	8.0±1.8	<0.001
Maximum tricuspid regurgitation flow, m/s*	1.95±0.42	1.80±0.56	1.90±0.51	0.113
Left atrial volume index, mL/m^{2}†				
Total	30.2±6.3	30.0±7.0	29.8±6.8	0.486
Men	31.1±6.6	30.7±8.0	30.2±6.9	0.321
Women	29.6±6.0	28.8±5.0	28.9±6.7	0.376
LV mass index, g/m$^{2.7}$‡				
Total	28.7±6.2	31.5±6.8	31.3±6.7	<0.001
Men	29.8±6.7	31.5±6.7	31.3±7.2	0.077
Women	27.9±5.7	30.9±7.1	32.3±5.5	<0.001
LV mass index, g/m^{2}‡				
Total	65.2±13.6	65.9±14.0	67.4±14.5	0.047
Men	69.9±15.1	71.5±13.6	69.3±15.5	0.800
Women	61.5±11.1	63.7±13.4	62.9±10.8	0.326
LV diastolic function according to 2016 guidelines (normal, indeterminate, abnormal), n (%)	162/162/42 (44.3/44.3/11.5)	25/67/19 (22.5/60.4/17.1)	38/92/32 (23.5/56.8/19.8)	<0.001
Systolic LV function				
LV ejection fraction, %§	60.7±2.5	60.2±2.6	59.7±3.5	0.001
S' septal, cm/s	7.5±1.3	7.2±1.3	7.5±1.7	0.931
S' lateral, cm/s	8.8±2.0	8.7±2.1	8.5±1.9	0.031
Other measures LV diastolic function				
Early peak velocity, m/s	0.68±0.15	0.66±0.14	0.67±0.14	0.540
Active peak velocity, m/s‖	0.66±0.15	0.72±0.16	0.73±0.15	<0.001
E/A ratio‖	1.04 [0.87–1.27]	0.90 [0.76–1.08]	0.91 [0.78–1.10]	<0.001
Deceleration time E-peak, ms	190±34	200±35	201±36	<0.001
Isovolumetric relaxation time, ms¶	94±20	100±23	95±21	0.200
S/D ratio#	1.38±0.31	1.43±0.35	1.47±0.31	0.004
e′ septal, cm/s	8.4±2.1	7.0±1.7	7.1±1.7	<0.001
a' septal, cm/s	9.8±1.8	9.8±1.7	10.1±1.9	0.166
e′ lateral, cm/s	10.7±2.5	9.4±2.6	8.9±2.2	<0.001
a' lateral, cm/s	10.6±2.4	11.2±2.4	11.3±2.3	0.001
Wall motion abnormalities, n yes (%)	0 (0.0)	1 (0.9)	3 (1.9)	0.012
Valvular dysfunction, moderate or severe, n (%)	23 (6.3)	7 (6.3)	8 (4.9)	0.573

Data are presented as mean±SD, median [interquartile range], or frequency (%) as appropriate. Data present the tissue Doppler imaging echocardiography population for regression Models 1 to 3. Linear trend was tested with ANOVA or χ^2 test as appropriate. E/A indicates peak flow velocity E/peak flow velocity A; LV, left ventricular; NGM, normal glucose metabolism; S/D, systolic/diastolic pulmonary peak inflow velocity; and T2D, type 2 diabetes mellitus.

Numbers for specific variables (total, NGM/prediabetes/T2D) are:

*Maximum tricuspid regurgitation flow 636, 366/110/160.

†Left atrial volume index 637, 366/109/162, men 339, 159/66/114, women 298, 207/43/48.

‡LV mass index 634, 363/110/161, men 338, 157/68/113, women 296, 206/42/48.

§LV ejection fraction 634, 364/109/161.

‖Active peak velocity and E/A ratio 636,366/110/160.

¶Isovolumetric relaxation time 634, 362/110/162.

#S/D ratio 634, 364/111/159.

Table 3. Associations Between Measures of LV Diastolic Function and Cardiorespiratory Fitness

	Model	Normal Glucose Metabolism, N=380/366			Prediabetes, N=115/111			Type 2 Diabetes Mellitus, N=177/162		
		B	95% CI	*P* Value	B	95% CI	*P* Value	B	95% CI	*P* Value
Average E/e′ ratio	1	−0.057	−0.084 to −0.030	<0.001	−0.047	−0.084 to −0.011	0.012	−0.040	−0.075 to −0.006	0.021
	2	−0.044	−0.071 to −0.016	0.002	−0.030	−0.072 to 0.012	0.156	−0.037	−0.072 to −0.001	0.043
	3	−0.033	−0.060 to −0.007	0.014	−0.015	−0.055 to 0.025	0.450	−0.028	−0.059 to 0.003	0.077
Average e′, cm/s	1	0.035	0.008 to 0.062	0.012	0.060	0.014 to 0.106	0.011	0.013	−0.032 to 0.057	0.570
	2	0.013	−0.016 to 0.042	0.388	0.040	−0.016 to 0.095	0.158	−0.010	−0.057 to 0.037	0.662
	3	0.009	−0.018 to 0.037	0.501	0.028	−0.023 to 0.079	0.280	−0.014	−0.055 to 0.026	0.487
Maximum tricuspid regurgitation flow, m/s	1	0.166	0.049 to 0.283	0.005	0.032	−0.128 to 0.191	0.694	0.034	−0.121 to 0.190	0.665
	2	0.137	0.023 to 0.252	0.019	−0.054	−0.213 to 0.134	0.653	−0.021	−0.175 to 0.133	0.785
	3	0.114	0.007 to 0.222	0.037	−0.064	−0.218 to 0.090	0.411	−0.021	−0.153 to 0.111	0.754
Left atrial volume index, mL/m^2	1	0.017	0.010 to 0.025	<0.001	−0.003	−0.015 to 0.010	0.674	0.003	−0.008 to 0.014	0.516
	2	0.015	0.008 to 0.022	<0.001	−0.007	−0.021 to 0.008	0.357*	0.001	−0.009 to 0.012	0.804*
	3	0.014	0.007 to 0.021	<0.001	−0.006	−0.018 to 0.007	0.358	−0.002	−0.011 to 0.007	0.618
LV mass index, g/m$^{2.7}$	1	0.005	−0.003 to 0.013	0.224	−0.002	−0.015 to 0.011	0.722	−0.009	−0.020 to 0.002	0.097
	2	0.009	0.001 to 0.017	0.035	0.001	−0.013 to 0.015	0.857	−0.006	−0.017 to 0.005	0.259*
	3	0.015	0.008 to 0.023	<0.001	0.009	−0.004 to 0.022	0.166	0.001	−0.009 to 0.010	0.859
Diastolic function 2016 guidelines										
Indeterminate	1	0.009	−0.104 to 0.123	0.872	−0.204	−0.408 to 0.001	0.051	−0.156	−0.339 to 0.027	0.095
	2	0.050	−0.061 to 0.160	0.374	−0.208	−0.422 to 0.005	0.055	−0.115	−0.302 to 0.073	0.229
	3	0.095	−0.009 to 0.199	0.074	−0.144	−0.345 to 0.057	0.157	−0.064	−0.227 to 0.100	0.441
Abnormal	1	0.100	−0.061 to 0.160	0.055	−0.115	−0.386 to 0.157	0.404	−0.110	−0.342 to 0.122	0.350
	2	0.165	−0.004 to 0.335	0.055	−0.053	−0.329 to 0.224	0.706	−0.065	−0.301 to 0.170	0.229
	3	0.178	0.019 to 0.337	0.028	−0.022	−0.280 to 0.235	0.862	−0.056	−0.260 to 0.149	0.590

N=672 or 639 for the 2-dimensional or tissue Doppler imaging echocardiography study population, respectively. The unstandardized regression coefficients (B) represent the difference in cardiorespiratory fitness in W_{max} per kilogram per 1-unit higher level of measure of diastolic function, and for diastolic function according to 2016 guidelines vs normal diastolic function. Model 1: age, sex, height. Model 2: Model 1+prior cardiovascular disease, smoking status, alcohol use, total-to-HDL-cholesterol ratio, triglycerides, use of lipid-modifying medication, estimated glomerular filtration rate, health status, office systolic pressure, use of antihypertensive medication, albuminuria. Model 3: Model 2+waist. HDL indicates high-density lipoprotein; LV, left ventricular; and W_{max}, estimated maximum power output.

*$P_{interaction}$ <0.07, represents the *P* value of the interaction effect between measures of diastolic function and prediabetes as compared with normal glucose metabolism in the association with cardiorespiratory fitness.

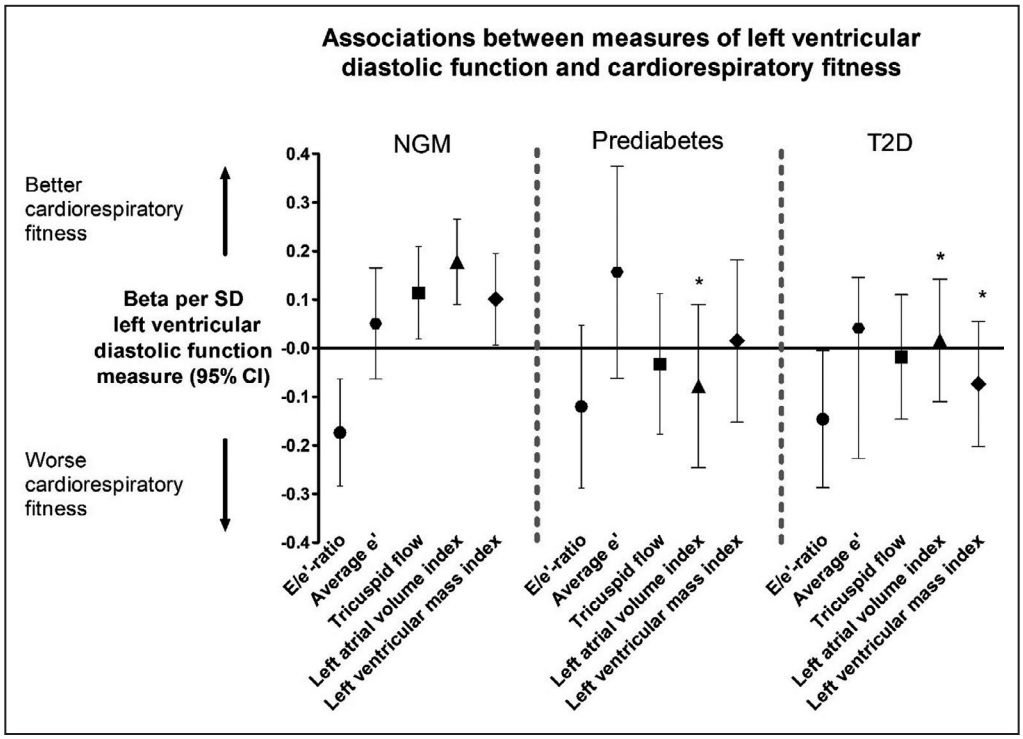

Figure. Associations between measures of left ventricular (LV) diastolic function and cardiorespiratory fitness.
The standardized regression coefficients represent the standardized difference in cardiorespiratory fitness per standard deviation higher measure of LV diastolic function in Model 2. Higher measures of LV diastolic function, apart from average e′, indicate deteriorating LV diastolic function. Model 2: adjusted for age, sex, height, prior cardiovascular disease, smoking status, alcohol use, lipids, lipid medication, estimated glomerular filtration rate, health status, office systolic pressure, antihypertensive medication, albuminuria. *$P_{interaction}$ <0.07 represents the *P* value of the interaction effect between measures of diastolic function and (pre)diabetes as compared with normal glucose metabolism in the association with cardiorespiratory fitness. Circle represents the standardized regression coefficient of E/e'-ratio; hexagram represents the standardized regression coefficient of Average e'; square represents the standardized regression coefficient of tricuspid flow; triangle represents the standardized regression coefficient of left atrial volume index; diamond represents the standardized regression coefficient of left ventricular mass index. NGM indicates normal glucose metabolism; and T2D, type 2 diabetes mellitus.

If we repeated the analyses between measures of LV diastolic function and CRF in the total population, associations were not materially altered compared with the associations in NGM, but the associations between LAVI and LVMI were attenuated in effect size and significance, because of a significant interaction between those measures and prediabetes in their association with CRF (Table S7).

Associations between measures of LV diastolic function and CRF were not materially altered in the following scenarios (Tables S8 through S12): when we replaced LAVI with nonindexed left atrial volume; when we replaced LVMI indexed by height with LVMI indexed by body surface area or LV mass (Table S8); when we replaced CRF as W_{max} per kilogram by CRF as the percentage of the predicted W_{max} (Table S9); when we additionally adjusted for moderate-to-vigorous physical activity; when we restricted the analyses to individuals without prior cardiac disease or without functional mobility limitations; when we replaced office systolic pressure with office diastolic pressure, presence of hypertension, or 24-hour ambulatory systolic or diastolic pressure; when we additionally adjusted for renin-angiotensin system inhibitors or β-blockers; or when we replaced waist with body mass index or weight (Tables S10 through S12). In addition, in men as compared with women, associations between measures of LV diastolic function and CRF did not statistically significantly differ ($P_{interactions}$ >0.10; Table S13).

DISCUSSION

In this population-based study, structural and functional measures of LV diastolic function were differentially associated with CRF over the strata of GMS, apart from average E/e′ ratio, which was inversely associated with CRF in all individuals. We found positive associations of maximum tricuspid regurgitation flow

and structural measures of LV diastolic function with CRF in individuals with NGM, but not in those with (pre)diabetes. These associations were independent of cardiovascular risk factors and lifestyle factors and remained unchanged after excluding individuals with prior cardiac pathology. Taken together, deteriorating LV diastolic function may contribute to the pathophysiological process of impaired CRF in the general population, although the effect was small. In addition, our results suggest that the differential effects over the strata of glucose metabolism are the consequence of cardiac structural adaptation to effectively increase CRF in NGM, but not in (pre)diabetes.

Previous population-based studies not stratified according to (pre)diabetes have investigated the association between structural and/or functional measures of LV diastolic function and CRF.[7–13] However, these studies are difficult to compare because they quantified LV diastolic function heterogeneously. Nevertheless, our study is in line with previous population-based studies that have reported inverse associations between several functional measures of LV diastolic function and CRF[7,8,10,11] and a positive association between a structural measure of LV diastolic function and CRF,[7] but not with others that have reported a negative association between structural measures of LV diastolic function and CRF[9,12] (for details see Table S1). The latter might be explained by the fact that these studies were performed in populations at high risk of CVD only.[9,12] Our study extends previous findings to assessment of the association between LV diastolic function and CRF, with both structural and functional measures of LV diastolic function,[14] in a relatively large population-based cohort of individuals aged 40 to 75 years stratified according to (pre)diabetes and with adjustment for multiple confounders.

Maladaptive cardiac structural alterations may be of hemodynamic and/or microvascular origin.[1] For instance, patients with heart failure with preserved ejection fraction are known to have lower CRF in whom diastolic filling is delayed, slowed, shortened, or associated with elevated LV pressures, leading to reduced ability to enhance transmitral flow and accelerate diastolic filling during exercise.[1] Conceivably, a similar mechanism may also be operative in individuals with subclinical LV diastolic dysfunction in the general population and might, as shown in previous studies,[14,15] be most sensitively detected by the functional measure of average E/e′ ratio.

Inadequate alterations in structural LV diastolic function measures could represent impairment of long-term cardiac hemodynamic function and perfusion. However, physiological cardiac adaptations also involve an increase of tricuspid flow,[30] an increase in LAVI,[31] and an increase in LVMI,[32] questioning their value as markers of early diastolic dysfunction. These adaptations may explain our findings that tricuspid flow and structural measures of LV diastolic function were positively associated with CRF in NGM. The absence of such associations in (pre)diabetes suggests either an absence of these physiological adaptations or early diastolic dysfunction that reverses the original physiological adaptation in (pre)diabetes.

Alternatively or additionally, subclinical LV diastolic dysfunction and CRF may share common risk factors, which over time produce alterations in both entities independently of each other. However, we adjusted extensively for potential confounders such as hypertension, smoking, and other cardiovascular risk factors, which therefore are unlikely explanations for the associations we observed. Still, we cannot exclude that other lifestyle factors (eg, dietary habits), which were not included in the analyses, might play a role in the association between LV diastolic function and CRF.[33]

The absence of a cardiac structural adaptation response in (pre)diabetes might be explained by the existence of preclinical hyperglycemia-driven diabetic cardiomyopathy.[3] Hyperglycemia affects the structures of the heart and results in myocardial fibrosis, with accumulation of advanced glycation end products in the myocardium; in increased myocardial content of free radicals and oxidants that decrease nitric oxide levels, worsen endothelial function, and induce myocardial inflammation; in elevation of free fatty acids and their oxidation products that may have direct toxic effects on the myocardium; and in altered intracellular calcium homeostasis that leads to myocardial dysfunction.[3] In addition, insulin resistance and hyperinsulinemia may contribute to LV hypertrophy,[34] and impaired glucose control and insulin resistance may lead to autonomic dysfunction and consequent myocardial hypertrophy and fibrosis.[34] Furthermore, the structure and function of the heart may be indirectly affected via alterations in vascular function (eg, microvascular function).[35] Because of synergy among these risk factors,[4] the presence of diabetic cardiomyopathy could aggravate LV diastolic function, or alternatively, it could inhibit an adequate structural adaptation.

The present study contributes to our understanding of the association between structural and functional measures of LV diastolic dysfunction and CRF in a population-based cohort stratified according to (pre)diabetes. First, we were able to accurately examine CRF and measures of LV diastolic function through a submaximal ergometer test instead of questionnaires[20] and the use of continuous structural and functional measures, in addition to a clinical cutoff definition of LV diastolic function according to recent guidelines.[14] Second, we adjusted for an extensive series of potential confounders including CVD risk factors such as systolic blood pressure and use of antihypertensive

medication. Risk of overadjustment bias[24] (in Model 3) was small, because associations were at most slightly attenuated by adjustment for waist. Moreover, associations remained after excluding individuals with prior coronary heart disease, atrial fibrillation, wall abnormalities, and significant valvular pathology, indicating a role for LV diastolic function in CRF in individuals without cardiac disease. Third, although reversed causality is biologically not unlikely,[36,37] our results were not materially altered when we additionally adjusted the analyses for physical activity.

Strengths of our study include its population-based design with oversampling of individuals with T2D, the consideration of prediabetes, and the use of extensive phenotyping, which allowed us to adjust for extensive series of CVD risk factors including 24-hour ambulatory blood pressure. Importantly, a broad array of additional analyses all gave consistent results.

Our study also has limitations. First, the cross-sectional design of the study does not allow us to draw strong causal inferences. However, from the association between LV diastolic dysfunction and CRF in patients with heart failure,[1,2] it follows that there is a strong prior likelihood that preclinical LV diastolic dysfunction to a certain extent may contribute to impairment in CRF. Second, the use of W_{max} per kilogram instead of percentage of predicted maximum may limit the clinical interpretation of the found associations. However, the use of the recommended and often used clinical formula by Jones et al[25,38] may also be questioned, because it is less precise in measuring differences in CRF and has led, in our study population, to an underestimation of the predicted value of W_{max} and consequently to an overestimation of the percent of the predicted W_{max} (Table S2). Nevertheless, when we replaced the outcome measure with the percentage of the predicted value of W_{max}, the results were not altered. Third, although average e′ could be a sensitive marker for early diastolic dysfunction, it was no longer associated with CRF after adjustment for potential confounders in our study. Therefore, the use of average e′ still needs further investigation in relation to CRF on population-based level as compared with E/e′ ratio.[1,14,15,39] Fourth, we may have underestimated associations between measures of LV diastolic function and CRF especially in T2D, because individuals who were excluded because of missing values had an adverse cardiometabolic risk profile, worse LV diastolic function, and lower CRF, the healthy participant effect (ie, sicker potential participants are less likely to participate, which is particularly likely for those with T2D). Fifth, LV strain imaging was not available in our study, which might be a potential alternative, but also an experimental measure for subclinical LV dysfunction to assess in association with CRF according to GMS.[40] Sixth, the generalizability of our findings to other populations can be questioned, but because of its population-based design, the results of our study may at least be generalized to middle-aged and older individuals with a similar cardiometabolic risk profile.

In conclusion, our population-based study shows that average E/e′ ratio as a measure of LV diastolic function was inversely associated with CRF, independently of cardiovascular risk factors, lifestyle factors, cardiac pathology, and GMS. Structural changes in left atrium and left ventricular muscle mass were positively associated with CRF in NGM but not in (pre)diabetes. Our findings suggest that deteriorating LV diastolic function may contribute to the pathophysiological process of impaired CRF in the general population. They also suggest that maximum tricuspid regurgitation flow and structural measures of LV diastolic function may not be accurate for the definition of early LV diastolic dysfunction in the general population. Moreover, structural adaptations of the left atrium and left ventricle may be different in (pre)diabetes as compared with NGM. Future prospective studies need to unravel the exact cardiovascular mechanisms to better understand the cardiac adaptation process in (pre)diabetes (eg, mechanisms of diabetic cardiomyopathy) in the early development of diastolic dysfunction and the usefulness of LV diastolic function as potential targets in preventive and therapeutic strategies for impaired CRF in the general population and in (pre)diabetes.

ARTICLE INFORMATION

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Author contributions: Dr Veugen participated in acquisition of data, contributed to study design, analyzed data, interpreted results, and wrote the article. Drs Linssen participated in acquisition of data, contributed to discussion, reviewed and edited the article. Dr Henry contributed to study conception, study design, analyzed data, interpreted results, and reviewed and edited the article. Dr Koster and Prof Kroon contributed to acquisition of data, discussion, reviewed and edited the article. Prof Stehouwer and Brunner-La Rocca contributed to conception and design, contributed interpretation of data, revised the article critically for important intellectual content. Prof Brunner-La Rocca is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final article.

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Supplementary Material

Data S1
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SUPPLEMENTAL MATERIAL

Data S1.

SUPPLEMENTAL METHODS

Echocardiography

Echocardiograms were obtained by research technicians according to a standardized protocol consisting of 2D, M-mode, color flow Doppler, pulsed and continuous wave Doppler, and Tissue Doppler recordings with use of echo equipment (Vivid E9 with 2.5-3.5 MHz and 4V transducer, GE Vingmed). All recordings were digitally stored and analyzed off-line (EchoPAC PC, version 112) by four researchers blinded to glucose metabolism status and other data.

Measures of left ventricular diastolic function

According to 2016 guidelines average E/e'-ratio and maximum tricuspid regurgitation flow were used as functional measures of left ventricular (LV) diastolic function, and left atrial volume index (LAVI) and left ventricular mass index (LVMI) were used as structural measures of left ventricular diastolic function.[14] In addition, left ventricular diastolic function was classified according to 2016 guidelines into normal, indeterminate or abnormal diastolic function.[14]

Mitral inflow velocities were obtained with pulsed-wave Doppler in the apical four-chamber view with placement of the sample volume at the tips of the mitral leaflets.[14] The peak flow velocity of the passive filling wave (E-wave) and active filling wave (A-wave) were measured. Pulsed Doppler tissue echocardiography was performed in the apical four-chamber view, with placement of the sample volume at the LV lateral and septal segment of the mitral annulus. At each site the peak myocardial systolic (S'), early (e') and late diastolic (a') longitudinal velocities were measured[14]. The mitral E/e' ratio's (septal, lateral and average) were calculated.

Continuous wave Doppler recordings of the tricuspid flow were obtained in an apical four-chamber view.[14, 41] Maximal tricuspid valve regurgitation velocity was measured and the maximal gradient was calculated with use of the Bernoulli equation.

End-systolic left atrial volume was estimated in the four- and two-chamber view with use of the modified Simpson's method.[42] Left atrial volume from biplane measurements was indexed to body surface area (BSA) calculated according to Mosteller.[42]

End-diastolic and end-systolic interventricular septum (IVSD, IVSS), posterior wall thickness (PWTD, PWTS), and LV diameters (LVEDD, LVESD) were determined in the parasternal long axis view, between the tip of the mitral leaflets and the chordae level perpendicular to the LV long axis. LV mass (LVM) was then calculated as $0.8*1.04*((LVEDD+IVSD+PWD)^3)-((LVEDD)^3)+0.6)$. LVM was indexed (LVMI) by height[2,7].[42-44]

In addition, left ventricular diastolic function was classified according to current guidelines (i.e. average E/e'>14, septal e'<7 or lateral e'<10, tricuspid regurgitation>2.8,

LAVI>34) into normal, indeterminate or abnormal diastolic function.[14] If ≥2 criteria were missing, diastolic function was classified as not specified.

Other echocardiography variables

End-diastolic and end-systolic LV volumes (LVEDV, LVESV) were determined in the apical four- and two-chamber view with use of the modified Simpson's method.[1] Systolic function was defined with the use of Simpson's LV ejection fraction calculated from biplane LVEDV and LVESV measurements.[42] The presence of wall motion abnormalities was evaluated by a trained researcher and checked by a senior cardiologist.

Valve function was investigated in a qualitative and semi-quantitative way. The global severity of valve stenosis and regurgitation was based on valve morphology, color Doppler images, transvalvular (mean) gradient and jet velocity with the criteria specified in current guidelines.[45-49] Significant valvular dysfunction was defined as any moderate or severe valve stenosis or regurgitation of the aortic, mitral, tricuspid or pulmonary valve or the presence of a valve prothesis.

From the E-wave and A-wave the E/A ratio was calculated[14]. Furthermore, the deceleration time (DT) of the E-wave was measured.[14]

Pulmonary venous inflow velocities were obtained with pulsed-wave Doppler in the apical four-chamber view with placement of the sample volume into the right upper pulmonary vein.[14] Peak systolic (S) and anterograde diastolic (D) velocities were measured.

Pulsed waved Doppler was obtained in the apical five-chamber view at the level of the LV outflow tract and the mitral inflow for assessment of closure to opening time (CTOT), isovolumetric contraction time (IVCT), ejection time (ET) and isovolumetric relaxation time (IVRT).[14]

Reproducibility of the analysis was assessed in 12 individuals (50% women; 57.8±11.5 years; four T2DM, four pre-diabetes) who were analysed by four observers. Intraclass correlation coefficients of observed agreement are described as below.

Variable	ICC (95% CI)	Variable	ICC (95% CI)	Variable	ICC (95% CI)
LVEDD	0.88 (0.75-0.96)	E peak mitral	0.95 (0.86-0.98)	S' LV septal	0.87 (0.48-0.97)
LVESD	0.94 (0.85-0.98)	A peak mitral	0.83 (0.53-0.95)	e' LV septal	0.96 (0.81-0.99)
IVSD	0.61 (0.29-0.85)	Dec. time E peak mitral	0.86 (0.71-0.95)	a' LV septal	0.87 (0.56-0.96)
PWTD	0.71 (0.45-0.89)	A peak duration mitral	0.92 (0.82-0.98)	S' LV lateral	0.86 (0.48-0.96)
LVEDV	0.59 (0.16-0.85)	S peak	0.86 (0.53-0.96)	e' LV lateral	0.93 (0.66-0.98)
LVESV	0.66 (0.23-0.88)	D peak	0.88 (0.62-0.96)	a' LV lateral	0.61 (0.14-0.87)
Left atrial volume	0.83 (0.59-0.94)	Tricuspid regurgitation	0.70 (0.44-0.88)		

The data are given in intraclass correlation coefficients (ICC) with their 95% confidence interval (95% CI). For clarification of other abbreviations see previous text.

Sub-maximal cycle ergometer test: cardiorespiratory fitness

The sub-maximal cycle ergometer test to determine cardiorespiratory fitness (CRF) in W_{max} was performed as described previously.[19] The ergometer test and echocardiography were performed at the same clinical visit. As an objective measure of CRF estimated maximum power output adjusted for body mass (W_{max}/kg) was used.[20, 21] W_{max} was estimated from a graded sub-maximal exercise protocol performed on a cycle ergometer system (CASETM version 6.6 in combination with e-bike, GE Healthcare, Milwaukee, WI, USA). Exclusion criteria for the sub-maximal cycle ergometer test were: having suffered from cardiovascular disease three months prior to the ergometer test, having an resting ECG with previously unknown abnormalities, having severe hypertension (SBP ≥180 and/or DBP ≥110), or being in the possession of an ICD/pacemaker. Participants eligible for the test were fitted with a blood pressure cuff on the upper left arm (Suntech Tango+TM, SunTech Medical, Inc. Morisville, NC, USA) and electrodes on the thorax to provide continuously a 12-leads ECG. In addition, (percentage of) predicted W_{max} was calculated by the formula of Jones et al.[25, 50]

As described previously,[19] the protocol consisted of a short warm-up period and at most 7 stages with increasing work load. Participants were instructed to cycle at a cadence of 60-70 rotation per minute (rpm) during a short familiarization period without any external workload. For the first exercise stage, external workload was set at 25 W. Every consecutive 2 minutes external workload was increased with 25 W. At the end of each stage, heart rate (HR) and blood pressure were measured. Further, the participant was asked to provide a rating of perceived exertion (RPE) on the 15-point Borg-scale; an interval scale ranging from 6 („no exertion at all") up to 20 („maximal exertion"). The exercise protocol was considered as „completed" when HR reached ≥ 85% of the estimated maximum HR (220-age) or when a RPE ≥ 17 was scored by the participant. If HR <85% or RPE <17 by the end of stage 7 (work

load of 175 W), the test was also stopped. The test could also be prematurely terminated on medical grounds or when the participant was unwilling to continue.

As described previously[19], submaximal values of HR and RPE with workload from each stage were extrapolated to 100% of maximum HR or an RPE of 20 and corresponding workload (=W_{max}) using individual linear regression models. Using RPE to predict W_{max} overcomes the issue that certain medical conditions, such as autonomous neuropathy and medication use (e.g. beta blockers) may affect the linear association of HR with power output. Consequently, this protocol is suitable for participants who otherwise would have been excluded from exercise testing[51]. A previous substudy of The Maastricht Study demonstrated that estimated Wmax using HR (W_{max} when HR reached 85%) was comparable to W_{max} based on RPE (W_{max} when a RPE ≥ 17 was scored).[19]

As described previously,[19] W_{max} was calculated from HR values if the test was completed based on HR, i.e. HR≥ 85% of estimated HR_{max}. W_{max} was calculated from RPE values if the test was completed based on RPE, i.e. RPE ≥ 17. In addition to completed tests, W_{max} from uncompleted tests was calculated from HR if ≥ 75% of HR_{max} was achieved and W_{max} was calculated from RPE values if an RPE ≥ 15 was scored. A previous sub study of The Maastricht Study demonstrated that estimations of W_{max} from these lower ranges of HR and RPE were found to be similar to completed tests.[19] Tests where both 75% of HR_{max} and RPE15 were not achieved were considered as invalid.

Covariates

We assessed fasting glucose, glycated hemoglobin (HbA1c), glucose metabolism status, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) cholesterol, total-to-HDL cholesterol ratio, triglycerides, body mass index (BMI), office blood pressure, 24-hour ambulatory blood pressure, medication use (glucose-lowering, antihypertensive and lipid-modifying), smoking status (never, former, current), alcohol consumption (non, low, high), medical cardiovascular history, serum creatinine, serum cystatin C, 24-hour urinary albumin excretion, educational level (low, intermediate, high) and (self-reported) physical activity as described previously.[18, 19, 22, 23] Glucose metabolism status was classified as described previously[18, 52]. For the present study impaired fasting glucose and impaired glucose tolerance were combined into prediabetes. Hypertension was defined as an office systolic pressure ≥ 140 mmHg, an office diastolic pressure ≥ 90 mmHg and(or) the use of antihypertensive medication.[18, 53] Alcohol consumption was classified as non-, low- (≤7 glasses per week for women; ≤14 glasses per week for men), or high-consumers (≥7 glasses per week for women and ≥14 glasses per week for men). Prior cardiovascular disease was defined as a self-reported history of myocardial infarction, cerebrovascular infarction or hemorrhage, and(or) vascular surgery (including percutaneous angioplasty) of the coronary, abdominal, peripheral

or carotid arteries. Prior coronary heart disease was defined as either 12-lead resting ECG signs of prior myocardial infarction (Minnesota code 1-1-1 to 1-2-8[54]) and/or self-reported history of myocardial infarction. Presence of current atrial fibrillation or atrial flutter was classified on the 12-lead resting electrocardiogram by The Minnesota Code Classification System for electrocardiographic findings (code 8-3-1 or 8-3-2[54]). Estimated glomerular filtration rate was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation based on both serum creatinine and serum cystatin C.[55] Presence of micro- or macro-albuminuria (an urinary albumin excretion of 30-300mg or an urinary albumin excretion of >300mg per 24 hours,[56] respectively) was dichotomized. Level of education was assessed during the cognitive assessment and was classified into eight categories commonly used in the Netherlands:[57] 1) no formal education; 2) primary education; 3) lower vocational education; 4) intermediate general secondary education; 5) intermediate vocational education; 6) higher general secondary education; 7) higher vocational education; and 8) university level of education. For the present study, education level was further classified into low (level 1 to 3), intermediate (level 4 to 6) and high (level 7 to 8).[58] Moderate-to-vigorous physical activity in hours per week was assessed with a modified version of the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire.[59]

Table S1. Overview of population-based studies of the associations between measures of LV diastolic function and cardiorespiratory fitness.

Reference	Study design	Study population, N	Population characteristics	Echocardiographic measures of diastolic function reported	Measure of cardiorespiratory fitness reported	Adjustments reported	Main results: association of measures of diastolic function with cardiorespiratory fitness
Leite et al. (2017)[11]	Asymptomatic volunteers from community-based population aged ≥ 18 years without moderate-to-severe valvular disease, pulmonary hypertension, and history of cardiac disease.	20	Mean age 51 years; 13 men / 7 women; 0 with diabetes.	Left atrium function by 2D speckle tracking (LA conduit strain rate); LVEDD, LVMI, LAVI, E/A-ratio, deceleration time, E/e'-ratio, S/D-ratio.	Peak oxygen uptake (VO2) via cardiopulmonary exercise testing by treadmill.	Unadjusted correlation (r); multivariable linear regression (beta) with adjustment for E/e' –ratio and age (only reported for significant associations).	After adjustment only LA conduit strain rate was associated with peak VO2. E/e' - peak VO2: r=-0.72; p<0.01. LA function: LA conduit strain rate – peak VO2: r=-0.82, p<0.01; beta= -0.69, p=0.02. Other measures (unadjusted significantly associated): LVEDD – peak VO2: r=0.47, p=0.04. After adjustment other measures were not associated with peak VO2.
Pellet et al. (2013)[12]	Community-based Louisiana healthy ageing study in individuals aged ≥60 years who underwent echocardiography and performed the CS-PFP-10 test without active atrial fibrillation and a calculated mitral valve area of less than 1.5 cm^2.	36	Age range 62-101 years; 15 men / 21 women; 6 with diabetes.	LAVI, pulmonary venous atrial reversal velocity, E/A- ratio, mitral a-wave duration, deceleration time, atrial reverse wave duration, E/e'-ratio and LVMI.	10-item continuous scale physical performance test (CS-PFP-10) with domains balance and coordination, endurance, lower body strength, upper body strength, upper body flexibility.	Correlation (r) adjusted for age and sex and after correction for multiple comparisons p<0.001).	After adjustment only LAVI was associated with total CS-PFP-10 and the endurance domain. LAVI – total CS-PFP-10: r=- 0.59, p=0.0005. LAVI – endurance domain: r=-0.63, p=0.0002. After adjustment other measures were not associated with the CS-PFP-10 score (after correction for multiple comparisons).
Perry et al. (2011)[13]	Community-dwelling older adults aged ≥65 years without heart failure, valvular disease and atrial fibrillation.	89	Mean age 74 (range 65-93) years; 41 men / 48 women; 6 with diabetes.	Normal diastolic function (E/A-ratio 0.75-1.5 and E/e'-ratio <10), grade I (E/A-ratio <0.75, regardless of E/e'-ratio), II (E/A-ratio 0.75-1.5 and E/e'-ratio >10) and III (E/A-ratio >1.5 and E/e'-ratio >10) dichotomized into LV diastolic dysfunction no/ yes (grade I-III).	6 minute walking distance (6MWD)	Unadjusted correlation (r); multivariable linear regression adjusted for age, cardiovascular morbidity, sex, race, BMI, systolic blood pressure	After adjustment LV diastolic dysfunction was not associated with 6MWD. LV diastolic dysfunction – 6MWD: 1013 versus 1128 feet; unadjusted r=-0.25 p=0.017; adjusted r=-0.44, p=0.365.
Okura et al. (2000)[10]	Healthy individuals who received medical checkup in Kobe Rehabilitation Hospital without atrial fibrillation, long-term use of medication, hypertension, diabetes mellitus, cardiovascular disease, exercise-limiting musculoskeletal, hematologic or pulmonary	160	Mean age 55 years; 101 men / 59 women; 0 with diabetes (excluded).	E-peak, A-peak, E/A-ratio, deceleration time, LVEDV, LV mass. No TDI measurements.	Metabolic equivalent (METs) via exercise testing by treadmill.	Unadjusted correlation (r); multivariable regression (beta (95% CI) with E/A-ratio, vital capacity, BMI, age, hemoglobin (only reported for significant associations).	After adjustment only E/A ratio was associated with METs. E/A-ratio – METs: r=0.58, p<0.0001); beta=1.385 (0.796;1.975), p<0.001. Other measures (unadjusted significantly associated): E-peak – METs: r=0.24, p=0.0024. A-peak – METs: r=-0.51, p<0.0001. Deceleration time – METs: r=-0.30, p=0.0002. LVEDV – METs: r=0.19, p=0.0172.

	diseases, and who had no positive results for ischemic heart disease by treadmill exercise test.						After adjustment the other measures were not associated with METs.
Lauer et al. (1995)[9]	Individuals from Framingham Offspring (Heart) study without coronary artery disease, congestive heart failure, valvular heart disease, atrial fibrillation, bundle branch block, pre-excitation, use of digoxin and beta-blockers.	3,026	Mean age men 43 years, women 43 years; 1,408 men / 1,618 women; 32 men with diabetes and 14 women with diabetes.	LV mass indexed by height. No TDI measurements.	Metabolic equivalent (METs) via exercise testing by treadmill.	Multivariable linear regression analyses adjusted for age, BMI, cigarette smoking, beta-blocker therapy, hypertension treatment, number of awake sedentary hours spent per day.	Sex-stratified analyses showed that the association between LV mass index and exercise capacity in METs remained significant after adjustment (p=0.0001 for both sexes; numbers not given). Presence of LV hypertrophy was associated with reduced exercise capacity.
Genovesi-Ebert et al. (1994)[8]	Volunteers from medical and paramedical staff university Pisa and airport staff and borderline to severe essential hypertensive patients.	51	Mean age 45.8 years; 43 men / 8 women; diabetes status unknown. 20 volunteers and 34 patients.	A-peak, A/E-ratio, early filling fraction (ratio between velocity-time integral under the E-peak and that of the whole diastolic flow.	Exercise time via exercise testing by cycle ergometer.	Multivariable linear regression analyses with diastolic blood pressure, LV mass index, age and either A-peak, E/A-ratio or early filling fraction (only reported for significant associations).	After adjustment only A-peak and early filling fraction were associated with exercise time. A-peak – exercise time: r=-0.54, p<0.0001; beta=-0.077, p<0.05. Early filling fraction: r=0.51, p<0.001; beta=11.807, p<0.05. Other measures (unadjusted significantly associated): A/E-ratio – exercise time: r=-0.46, p<0.001. LV mass – exercise time: r=-0.31, p<0.025. LV mass index – exercise time: -0.38, p<0.01. After adjustment the other measures were not associated with exercise time.
Vanoverschelde et al. (1985)[7]	Normal sedentary volunteers and endurance athletes.	66	57 normal sedentary volunteers: mean age 36 (range 20-76) years, 9 endurance athletes: mean age 37 (range 26-51) years; 40 men / 26 women; diabetes status unknown.	E/A-ratio, E-peak, A-peak, LVEDV index, IVRT, LV mass.	Peak oxygen uptake (VO2) via exercise testing by cycle ergometer.	Stepwise multivariable regression analyses with E/A-ratio, E-peak, A-peak, LVESV index, IVRT, systolic blood pressure at maximum exercise, age, LVEDV index, heart rate at maximum exercise, LV mass, sex, resting heart rate, resting stroke index, LV ejection fraction, end-systolic wall stress, radius/thickness-ratio and mean velocity of fiber shortening	After adjustment only E/A-ratio and LVEDV index were associated with VO2. E/A-ratio – VO2: r=0.87. LVEDV index – VO2: r=0.51; Other measures (unadjusted significantly associated): E-peak – VO2: r=0.78, p<0.001; A-peak – VO2: r=-0.73, p<0.001. IVRT – VO2: r=-0.61, p<0.001. LVEDV index – VO2: r=0.51, p<0.001. LV mass – VO2: r=0.42, p<0.001. After adjustment the other measures were not associated with VO2.

Studies in patients without cardiac ischemia referred for exercise testing

Reference	Study design	Study popu-lation, N	Population characteristics	Echocardiographic measures of diastolic function reported	Measure of cardiorespiratory fitness reported	Adjustments reported	Main results: association of measures of diastolic function with cardiorespiratory fitness
Otto et al. (2011)[16]	Patients who underwent exercise testing and echocardiography within 30 days with retrospectively low risk for coronary artery disease.	640	Mean age 49 years; 384 men / 256 women; 50 with diabetes.	LV mass index, LVEDD, E-peak, A-peak, E/A-ratio, deceleration time, e'-peak, E/e'-ratio. E/e'-ratio > 10. Presence of diastolic dysfunction: normal (E/A-ratio>0.8, e'>8cm/s, normal LA vol, E/e'-ratio not considered); Abnormal relaxation (E/A-ratio<0.8, e'<8 cm/s, variable LA vol, variable E/e'-ratio'); pseudonormal diastolic dysfunction (E/A-ratio>0.8, e'<8 cm/s, LA volume usually increased, and E/e'-ratio'>15), and restrictive diastolic dysfunction (E/A-ratio>1.8, e/ < 8cm/s, LA volume usually increased, and E/e'-ratio/ >15).	Metabolic equivalent (METs) < and ≥ 7 via exercise testing by treadmill.	Unadjusted comparisons of group METs < and ≥ 7; multivariable logistic regression (odds ratio (OR)) with adjustment from significant univariate analyses: age, sex, diabetes mellitus, hypertension, obesity, LV mass index, A-peak, E/A-ratio, e'-peak, S-peak, E/e'-ratio.	After adjustment only A-peak was associated with METs <7. A-peak unadjusted difference METs < and ≥ 7: p<0.001; OR 1.03, p<0.004. Other measures unadjusted significantly associated: LV mass index (p=0.011), A-peak (p<0.001), E/A-ratio (p<0.001), e'-peak (p<0.001), E/e'-ratio (p<0.001). After adjustment the other measures were not associated with METs <7. (unadjusted) E/e'-ratio > 10 was significantly higher in the MET <7 group vs MET ≥7 group (41.7% vs 9.4%, p=0.001), as was the presence of any degree of diastolic dysfunction (76.6% vs 34.1%, p=0.001).
Grewal et al. (2009)[17]	Patients who underwent exercise echocardiography according to the Bruce protocol without atrial fibrillation, moderate or severe valvular heart disease, ejection fraction <50% evidence of myocardial ischemia on the test, or had poor image quality.	2,867	Mean age normal diastolic function 53 years, mild dysfunction 67 years, moderate or severe dysfunction 66 years (N=1,784/785/298); 1,569 men / 1,298 women; 290 with diabetes.	Diastolic function categorized in normal, mild (impaired relaxation; E/A-ratio <0.75), moderate (pseudonormal; 0.75≤E/A-ratio≤1.5 and LAVI ≥28 mL/m^2 and E/e'-ratio ≥10), or severe (restrictive; E/A-ratio >1.5 and LAVI ≥28 mL/m^2 and E/e'-ratio ≥10) dysfunction. Resting E/e'-ratio ≥15. Postexercise E/e'-ratio ≥15. LVEDD, deceleration time, LA volume index.	Metabolic equivalents (METs) via exercise testing by treadmill.	Stepwise multivariable regression beta (95% CI) with normal/mild/moderate-severe diastolic function or E/e'-ratio ≥15, age, sex, pulse pressure, heart rate, BMI, coronary artery disease, diabetes mellitus, hypertension, previous or current smoker; and considered but not significant: ejection fraction, wall motion score index, LVEDD, deceleration time, LA volume index, hyperlipidemia, systolic blood pressure, beta-blocker use, calcium channel blocker use, angiotensin converting enzyme	After adjustment mild and moderate diastolic dysfunction and resting and postexercise E/e' ≥15 were associated with lower METs. Mild dysfunction vs normal – METS: beta -0.70 (-0.88;-0.46), p<0.001. Moderate or severe dysfunction vs normal – METs: beta -1.30 (-1.52;-0.99), p<0.001. Resting E/e'-ratio ≥15 – METs: -0.41(-0.70;-0.11), p=0.007. Postexercise E/e'-ratio ≥15 – METs: -0.41 (-0.70;-0.11), p=0.007. Other measures unadjusted significantly associated: LVEDD – METs: beta 0.08 (0.06;0.11), p<0.001. Deceleration time per 40 milliseconds – METs: beta -0.34 (-0.44;-0.26), p<0.001. LAVI >30 mL/m^2 – METs: beta -0.45 (-0.69;-0.26), p<0.001. After adjustment the other measures were not significantly associated with METs.

						inhibitor or angiotensin receptor blocker use.	
Skaluba et al. (2004)[15]	Patients who underwent exercise echocardiography aged >18 years without pacemaker, severe native valvular disease or prosthetic heart valves and evidence of cardiac ischemia on the test.	121	Mean age 55 years; 59 men / 62 women; 16 with diabetes.	E-peak, A-peak, e'-peak, a' –peak, e' /a'-ratio, E/e'-ratio, LVEDD, LA area, deceleration time, isovolumetric relaxation time.	Metabolic equivalent (METs) ≤ and >7 via exercise testing by treadmill.	Unadjusted correlation; multivariable logistic and linear regression with adjustment for hypertension, age, coronary artery disease, diabetes, BMI, chronic renal insufficiency, LV hypertrophy, prevalence of outcome.	Of all the echo and clinical parameters assessed, E/Ea had the best correlation with exercise capacity (r=-0.684, p<0.001) and was the strongest independent predictor of exercise capacity <= 7 METs by multivariate analysis (prevalence-corrected odds ratio=12.6, p<0.001). E/e'-ratio – METs: r=0.684, p<0.001. E/e'-ratio ≥10 – METs ≤7: unadjusted OR 18.2(4.8-24.9), p<0.001; adjusted OR 12.6(4.2-22.2), p<0.001). E/e'-ratio – METs (continuous): beta -0.441, p<0.001. Other measures unadjusted significantly associated: A-peak – METs: r=-0.290, p=0.001. e'-peak – METs: r=0.482, p<0.001. e'/a'-ratio – METs: r=0.450, p<0.001. After adjustment the other measures were not significantly associated with METs.

Abbreviations: A-peak, mitral late filling velocity peak; BMI, body mass index; CI, confidence interval; E-peak, mitral early filling velocity peak; IVRT, isovolumetric relaxation time; LA, left atrial; LAVI, left atrial volume index; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; , tissue Doppler imaging. e'-peak, a'-peak, S-peak, E/e'-ratio.

Table S2. General characteristics of the tissue Doppler imaging echocardiography study population according to tertiles of average E/e'-ratio

Average E/e' ratio	**Low [2.8-6.9]** (n=213)	**Middle [6.9-8.6]** (n=213)	**High [8.6-17.1]** (n=213)	**P-value**
Demographics				
Men, %	56	56	48	0.081
Age, years	56±9	60±8	62±7	<0.001
Educational level, low/middle/high, %	12.7/32.5/54.7	16.4/44.1/39.4	17.8/46.5/35.7	0.001
Glucose metabolism status, NGM/prediabetes/T2D, %	71.8/14.1/14.1	58.2/17.8/23.9	41.8/20.2/38.0	<0.001
Prior cardiovascular disease, %	8	12	18	0.001
Prior coronary heart disease,%	2	5	8	0.015
Current atrial fibrillation or flutter, %[a]	0.0	1.0	0.0	0.984
Blood pressure				
Office systolic pressure, mmHg	129±16	134±16	143±19	<0.001
Office diastolic pressure, mmHg	75±9	76±10	78±10	0.001
24-hour systolic pressure, mmHg[b]	116±11	118±11	121±12	<0.001
24-hour diastolic pressure, mmHg[b]	73±8	74±7	74±7	0.839
Hypertension, %	32	50	72	<0.001
Metabolic variables				
BMI, kg/m^2	25.4±3.1	26.4±3.6	27.9±3.8	<0.001
Waist, cm	92.1±10.7	94.7±11.5	97.7±12.2	<0.001
Total cholesterol, mmol/L	5.38±1.04	5.26±1.06	5.23±1.18	0.173
High-density lipoprotein, mmol/L	1.49±0.48	1.40±0.45	1.37±0.42	0.006
Low-density lipoprotein, mmol/L	3.36±0.90	3.23±0.96	3.18±1.04	0.052
Triglycerides, mmol/L	1.03[0.75;1.47]	1.18[0.85;1.73]	1.38[0.96;1.91]	<0.001
Total-to-HDL-cholesterol ratio	3.90±1.23	4.03±1.25	4.04±1.15	0.209
HbA1C, in %[c]	5.7±0.84	5.9±0.7	6.1±0.7	<0.001
Fasting plasma glucose, mmol/L	5.7±1.5	5.9±1.0	6.3±1.5	<0.001
Kidney function				
eGFR, ml/min 1.73m^2	92.3±14.6	87.9±14.1	86.1±15.0	<0.001
Albuminuria, %	3.8	5.2	12.2	0.001
Lifestyle variables				
Smoking status: never/former/current, %	35.7/48.8/15.5	35.2/49.8/15.0	31.9/55.4/12.7	0.885
Alcohol use: no/low/high, %	13.6/58.2/28.2	16.0/56.3/27.7	20.7/46.0/33.3	0.772
Moderate to vigorous physical activity, hours/week[d]	4.8[3.0;8.0]	5.0[3.0;8.3]	4.5[2.5;7.5]	0.439
Medication				
Anti-hypertensive medication, %	21	31	51	<0.001
RAS inhibitors, %	16	23	38	<0.001
Beta- blockers, %	7	16	24	<0.001
Diuretics, %	8	8	18	0.001
Calcium antagonists, %	4	4	10	0.005
Oral antidiabetics and/or insulin use	11	19	27	<0.001
Lipid-modifying medication, %	16	37	46	<0.001
Cardiorespiratory fitness (W_{max})	178.7±46.5	166.9±46.1	152.9±44.7	<0.001

Cardiorespiratory fitness adjusted for body mass (W_{max}/kg)	2.36±0.57	2.15±0.49	1.93±0.49	<0.001
Predicted cardiorespiratory fitness (predicted W_{max})	165.2±48.7	153.5±48.5	138.2±49.8	<0.001
Cardiorespiratory fitness (% of predicted W_{max})	113.9±30.8	114.8±30.8	119.4±38.7	0.188
Mobility limitation, %[e]	17	16	24	0.059

Data are presented as mean ± SD, median [interquartile-range] or frequencies (in %) as appropriate. Data present the tissue Doppler imaging echocardiography population for regression models 1-5. Linear trend was tested with ANOVA or chi-square test as appropriate. Abbreviations: eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein; NGM, normal glucose metabolism; RAS, renin angiotensin system ; T2D, type 2 diabetes.
Numbers for specific variables (total, NGM/prediabetes/ T2D) are [a]current atrial fibrillation or flutter 610, 200/203/207; [b]24-hour blood pressure measurements 590, 193/192/205; [c]HbA1c 638, 212/213/213; [d]moderate to vigourous physical activity 554, 190/178/186; [e]mobility limitation 636, 212/213/211.

Table S3. Echocardiographic characteristics of the tissue Doppler imaging echocardiography study population according to tertiles of average E/e' ratio

Averaged E/e' ratio	Low **[2.8-6.9]** (n=213)	Middle **[6.9-8.6]** (n=213)	High **[8.6-17.1]** (n=213)	P-value
Measures LV diastolic function				
Average E/e'-ratio	5.9±0.7	7.8±0.5	10.5±1.7	<0.001
e' average, cm/s	10.5±2.1	8.9±1.6	7.4±1.5	<0.001
Maximum tricuspid regurgitation flow, m/s[a]	1.90±0.42	1.86±0.45	1.96±0.52	0.135
LA volume index, ml/m^{2} [b]				
Total	29.8±6.6	30.0±6.6	30.4±6.5	0.309
Men	29.9±7.1	31.5±7.1	30.8±6.5	0.311
Women	29.7±6.1	28.2±5.2	30.1±6.4	0.506
LV mass index, gr/m$^{2.7}$ [c]				
Total	28.9±6.4	29.0±5.9	31.6±7.0	<0.001
Men	30.0±7.1	30.0±7.1	32.2±7.4	0.019
Women	27.4±4.9	27.8±5.7	31.1±6.5	<0.001
LV mass index, gr/m^{2} [c]				
Total	66.4±13.7	64.8±12.9	67.7±15.2	0.326
Men	70.3±14.7	68.6±13.5	71.4±16.6	0.651
Women	61.3±10.2	60.1±10.3	64.4±12.9	0.043
LV diastolic function according to 2016 guidelines (normal, indeterminate, abnormal), n (%)	114/86/12 (53.5/40.8/5.6)	78/103/32 (36.6/48.4/15.0)	33/131/49 (15.5/61.5/23.0)	<0.001
LV function				
Systolic LV function				
LV ejection fraction, %[d]	60.4±2.6	60.4±2.6	60.2±3.3	0.459
S' septal, cm/s	8.0±1.5	7.4±1.3	7.0±1.3	<0.001
S' lateral, cm/s	9.5±2.1	8.7±1.9	7.8±1.6	<0.001
Other measures LV diastolic function				
Early peak velocity, m/s	0.60±0.13	0.67±0.12	0.75±0.14	<0.001
Active peak velocity, m/s[e]	0.60±0.12	0.67±0.13	0.78±0.15	<0.001
E/A ratio[e]	0.99[0.82;1.25]	1.02[0.81;1.20]	0.92[0.79;1.13]	0.118
Deceleration time E-peak, msec	198±40	190±32	196±32	0.656
Isovolumetric relaxation time, msec[f]	95±20	96±22	95±22	0.946
S/D ratio[g]	1.39±0.33	1.41±0.31	1.44±0.32	0.096
e' septal, cm/s	9.1±2.1	7.7±1.6	6.6±1.5	<0.001
a' septal, cm/s[d]	10.0±1.9	10.0±1.7	9.6±1.9	0.039
e' lateral, cm/s	11.8±2.6	10.1±1.9	8.2±1.9	<0.001
a' lateral, cm/s[d]	10.9±2.5	11.0±2.3	10.8±2.4	0.830
Wall motion abnormalities, n yes (%)	3 (1.4)	0 (0.0)	1 (0.5)	0.219
Valvular dysfunction (moderate or severe), n (%)	7 (3.3)	13 (6.1)	18 (8.5)	0.024

Data are presented as mean ± SD, median [interquartile-range] or frequencies (in %) as appropriate. Data present the tissue Doppler imaging echocardiography population for regression models 1-5. Linear trend was tested with ANOVA or chi-square test as appropriate. Abbreviations: eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein; NGM, normal glucose metabolism; RAS, renin angiotensin system ; T2D, type 2 diabetes. Numbers for specific variables (total, NGM/prediabetes/ T2D) are [a]maximum tricuspid regurgitation flow 636, 213/211/212; [b]LA volume index 637, 212/212/213, men 339, 119/118/102, women 298, 93/94/111; [c]LV mass index 634, 212/210/212, men 338, 120/116/102, women 296, 92/94/110; [d]LV ejection fraction 634, 212/211/211; [e]active peak velocity and E/A ratio 636,213/210/213; [f]isovolumetric relaxation time 634, 212/209/213; [g]S/D ratio 634, 213/210/211.

Table S4. Clinical characteristics of the study population with tissue Doppler imaging echocardiography and individuals excluded from analyses due to missing values

	Normal glucose metabolism				Prediabetes				Type 2 Diabetes				Total study population			
	Included (N=366)	Number of missings $	Excluded (N=192)	P	Included (N=111)	Number of missings $	Excluded (N=77)	P	Included (N=162)	Number of missings $	Excluded (N=169)	P	Included (N=639)	Number of missings $	Excluded (N=438)	P
Demographics																
Men, %	43	0	45	0.673	61	0	57	0.571	70	0	67	0.492	53	0	56	0.448
Age, years	60±8	0	58±9	0.230	62±7	0	61±8	0.403	63±7	0	64±7	0.123	59±8	0	61±9	0.004
Educational level, low/middle/high, %*	10.7/39.2/50.1	1	9.9/38.5/51.6	0.933	17.1/44.1/38.7	0	20.8/40.3/39.0	0.783	25.9/43.2/30.9	0	30.8/47.9/21.3	0.135	15.7/52.2/43.3	1	19.9/42.5/37.7	0.094
Glucose metabolism status, NGM/prediabetes/T2D, %	-	-	-	-	-	-	-	-	-	-	-	-	57.3/17.4/25.4	0	43.8/17.6/38.6	<0.001
Prior cardiovascular disease, %	10	16	13	0.347	13	6	24	0.047	19	23	40	<0.001	13	45	24.9	<0.001
Prior coronary heart disease,%	3	1	7	0.036	6	0	7	0.959	9	1	17	0.020	5	2	11	<0.001
Current atrial fibrillation or flutter, %**	0.0	24	1.6	0.017	0.0	11	2.7	0.093	1.3	13	3.7	0.163	0.3	48	2.6	0.001
Blood pressure																
Office systolic pressure, mmHg	130±16	0	135±18	0.002	139±16	1	140±18	0.739	145±17	0	146±20	0.477	135±18	1	140±19	<0.001
Office diastolic pressure, mmHg	75±10	0	77±10	0.027	79±10	1	79±10	0.735	78±10	0	78±10	0.416	76±10	1	77±10	0.072
24-hour systolic pressure, mmHg†	116±11	43	118±11	0.010	121±12	19	123±15	0.388	122±11	33	124±14	0.219	118±11	95	121±13	<0.001
24-hour diastolic pressure, mmHg†	74±7	43	75±7	0.009	74±8	19	76±8	0.131	73±7	33	74±8	0.542	74±7	95	75±7	0.008
Hypertension, %	36	0	46	0.026	60	1	72	0.090	79	0	94	<0.001	52	1	69	<0.001
Metabolic variables																
BMI, kg/m^2	25.3±3.3	0	26.4±4.3	0.003	27.5±3.4	0	28.4±4.8	0.187	28.6±3.4	1	31.1±5.6	<0.001	26.5±3.7	1	28.6±5.4	<0.001
Waist, cm	90.4±10.5	2	93.5±12.6	0.004	98.2±10.6	0	99.7±13.6	0.410	102.7±10.1	1	109.4±15.4	<0.001	94.8±11.7	3	100.7±15.6	<0.001
Total cholesterol, mmol/L	5.59±0.99	3	5.53±1.11	0.487	5.46±1.09	0	5.51±1.29	0.767	4.49±0.92	1	4.39±1.10	0.395	5.29±1.09	4	5.08±1.26	0.006
High-density lipoprotein, mmol/L	1.54±0.49	3	1.39±0.35	<0.001	1.38±0.36	0	1.34±0.43	<0.001	1.19±0.32	1	1.10±0.33	0.010	1.42±0.45	4	1.27±0.38	<0.001
Low-density lipoprotein, mmol/L	3.54±0.87	3	3.58±1.00	0.644	3.39±0.99	0	3.42±1.10	0.644	2.53±0.78	1	2.50±0.97	0.728	3.26±0.97	4	3.13±1.12	0.056
Triglycerides, mmol/L	1.01 [0.75;1.40]	3	1.05 [0.81;1.49]	0.136	1.27 [0.88;1.78]	0	1.47 [1.07;2.19]	0.082	1.63 [1.16;2.08]	1	1.65 [1.16;2.36]	0.344	1.18 [0.83;1.74]	4	1.35 [0.92;1.95]	<0.001
Total-to-HDL-cholesterol ratio	3.95 ± 1.31	3	4.18±1.25	0.055	4.17±1.18	0	4.38±1.35	0.055	3.93±0.94	1	4.24±1.23	0.013	3.99±1.21	4	4.24±1.26	0.001
HbA1C, in %‡	5.5±0.3	3	5.6±0.3	0.005	5.8±0.4	1	5.8±0.4	0.005	6.7±0.9	0	7.1±1.1	<0.001	5.9±0.7	4	6.2±1.0	<0.001
Fasting plasma glucose, mmol/L§	5.2±0.4	1	5.3±0.4	0.043	6.0±0.5	0	5.9±0.6	0.043	7.6±1.7	1	8.2±2.4	0.017	5.9±1.4	2	6.5±2.1	<0.001
Kidney function																
eGFR, ml/min 1.73m^2	91.0±13.7	12	90.7±14.0	0.845	85.1±14.6	1	86.1±13.4	0.845	86.4±16.2	7	82.1±18.6	0.028	88.8±14.7	20	86.5±16.3	0.023
Albuminuria, %	3.3	5	4.3	0.552	4.5	1	10.5	0.112	17.3	7	20.4	0.477	7	13	12	0.012
Lifestyle variables																
Smoking status: never/former/current, %	38.9/45.5/15.6	5	30.5/48.1/21.4	0.085	28.8/61.3/9.9	3	29.7/54.1/16.2	0.401	27.8/57.4/14.8	15	19.5/64.3/16.2	0.222	34.3/51.3/14.4	23	26.3/55.2/18.6	0.014
Alcohol use: no/low/high, %	13.2/56.2/30.7	8	14.1/47.3/38.6	0.116	14.4/52.3/33.3	3	10.8/58.1/31.1	0.673	26.5/48.1/25.3	14	34.2/49.0/16.8	0.118	16.7/53.5/29.7	25	21.1/49.9/29.1	0.200

Moderate to vigorous physical activity, hours/week[#]	5.5 [3.0;9.0]	69	5.3 [3.0;8.5]	0.425	4.5 [2.69;7.1]	25	3.0 [1.5;6.8]	0.040	3.6 [2.3;10.0]	74	3.0 [1.5;5.8]	0.021	4.8 [3.0;8.0]	168	4.5 [1.5;7.0]	0.001
Medication																
Anti-hypertensive medication, %	20	0	25	0.169	40	0	53	0.065	63	0	82	<0.001	34	0	52	<0.001
RAS inhibitors, %	13	0	17	0.228	30	0	34	0.558	51	0	68	0.001	26	0	40	<0.001
Beta- blockers, %	6	0	12	0.046	19	0	27	0.176	33	0	37	0.448	15	0	24	<0.001
Diuretics, %	6	0	9	0.211	16	0	21	0.424	19	0	36	0.001	11	0	21	<0.001
Calcium antagonists, %	3	0	3	0.938	6	0	12	0.193	13	0	26	0.003	6	0	14	<0.001
Oral antidiabetics and/or insulin use	-	-	-	-	-	-	-	-	74	0	82	0.072	33	0	45	<0.001
Lipid-modifying medication, %	14	0	21	0.019	36	0	35	0.891	75	0	76	0.825	19	0	32	<0.001
Mobility limitation, %[††]	12	13	15	0.272	26	6	31	0.451	30	25	49	<0.001	19	44	31	<0.001
Average E/e'-ratio	7.6±1.9	106	8.1±2.6	0.055	8.6±2.4	42	8.3±2.3	0.647	8.9±2.3	96	10.0±3.5	0.013	8.1±2.2	244	8.9±3.0	0.001
e' average, cm/s	9.5±2.2	106	9.0±2.7	0.117	8.2±2.0	42	8.8±2.6	0.222	8.0±1.8	95	7.8±1.9	0.409	8.9±2.2	243	8.5±2.5	0.045
Diastolic LV function (normal, indeterminate, abnormal), n (%)	162/161/42 (44.4/44.1/ 11.5)	103	27/51/11 (30.3/57.3/ 12.4)	0.050	25/67/19 (22.5/60.4/ 17.1)	40	10/21/6 (27.0/56.8/ 16.2)	0.856	38/92/32 (23.5/56.8/ 19.8)	94	16/41/18 (21.3/54.7/ 24.0)	0.748	225/321/93 (35.2/50.2/ 14.6)	237	53/113/35 (26.4/56.2/ 17.4)	0.064
Cardiorespiratory fitness (W_{max})[§§]	168.9±48.6	85	158.7±46.8	0.055	168.8±46.1	42	159.8±57.8	0.055	158.1±42.7	101	156.3±50.6	0.771	166.2±46.9	228	158.1±49.8	0.034
Cardiorespiratory fitness adjusted for body mass (W_{max}/kg)[§§]	2.28±0.55	85	2.13±0.57	0.012	2.08±0.48	42	2.00±0.72	0.605	1.89±0.49	101	1.73±0.54	0.034	2.15±0.55	228	1.98±0.61	<0.001

Data are presented as mean ± SD, median [interquartile-range] or frequencies (in %) as appropriate. Data present the tissue Doppler imaging echocardiography study population for regression models 1-3. Significant difference between the tissue Doppler imaging echocardiography study population and excluded individuals with missing values in models 1 to 3 was tested by independent t-test or chi-square test as appropriate. Abbreviations: BMI, body mass index, eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein; MINI, mini-international neuropsychiatric interview; NGM, normal glucose metabolism; PHQ, patient health questionnaire; T2D, type 2 diabetes.
[$]=The total number of missings in the study population is listed here. For the covariates included in regression models 1 to 3, the number of individuals available in the excluded group was 192/77/162/438 for respectively normal glucose metabolism, prediabetes, type 2 diabetes and the total study population, minus the number of missings in the study population. For the covariates not included in regression models 1 to 3, the number of individuals available in the study population and available in the excluded group are indicated with footnotes [*] to [§§] for respectively normal glucose metabolism, prediabetes, type 2 diabetes and the total study population. *=Educational level was available in 365/111/162/638 in the study population and 192/77/169/438 in the excluded group; **=Current atrial fibrillation or flutter was available in 350/103/157/610 in the study population and 184/74/161/419 in the excluded group; [†]=24-hour blood pressure measurements were available in 340/101/149/590 in the study population and 175/68/149/392 in the excluded group; [‡]=HbA1c was available in 365/110/162/637 in the study population and 190/77/169/436 in the excluded group; [§]=Fasting plasma glucose was available in 366/111/162/639 in the study population and 191/77/168/436 in the excluded group; [#]Moderate to vigorous physical activity was available in 322/94/138/554 in the study population and 167/69/119/355 in the excluded group; [††]=Mobility limitation was available in 364/110/162 in the study population and 181/72/144/397 in the excluded group; [‡‡]=Diastolic LV function was available in 366/111/162/639 in the study population and in 89/37/75/201 in the excluded group; [§§]=in the excluded group 107/35/68/210 were excluded due to missing on echocardiographic analyses or covariates.

Table S5. Clinical characteristics of the study population with 2D echocardiography and individuals excluded from analyses due to missing values

	Normal glucose metabolism				Prediabetes				Type 2 Diabetes				Total study population			
	Included (N=380)	Number of missings $	Excluded (N=178)	P	Included (N=115)	Number of missings $	Excluded (N=73)	P	Included (N=177)	Number of missings $	Excluded (N=154)	P	Included (N=672)	Number of missings $	Excluded (N=405)	P
Demographics																
Men, %	42	0	48	0.232	59	0	60	0.876	68	0	70	0.813	52	0	58	0.043
Age, years	57±8	0	58±9	0.526	62±7	0	62±8	0.890	63±7	0	64±7	0.081	59±8	0	61±9	0.007
Educational level, low/middle/high, %*	10.6/38.8/50.7	1	10.1/39.3/50.6	0.984	16.5/43.5/40.0	0	21.9/41.1/37.0	0.650	24.9/46.9/28.2	0	32.5/44.2/23.4	0.277	15.4/41.7/42.9	1	20.7/41.5/37.8	0.053
Glucose metabolism status, NGM/prediabetes/T2D, %	-	-	-	-	-	-	-	-	-	-	-	-	56.5/17.1/26.3	0	44.0/18.0/38.0	<0.001
Prior cardiovascular disease, %	10	16	13	0.266	15	6	21	0.290	20	23	41	<0.001	13	45	25	<0.001
Prior coronary heart disease,%	3	1	7	0.050	6	0	7	0.835	10	1	16	0.097	6	2	10	0.003
Current atrial fibrillation or flutter, %**	0	24	1.8	0.011	0	11	2.9	0.079	1.2	13	4.1	0.098	0.3	48	2.8	<0.001
Blood pressure																
Office systolic pressure, mmHg	130±16	0	134±18	0.016	138±16	1	140±18	0.443	144±17	0	147±20	0.093	135±17	1	140±20	<0.001
Office diastolic pressure, mmHg	75±10	0	76±10	0.099	79±10	1	79±10	1.000	79±9	0	78±10	0.424	76±10	1	77±10	0.219
24-hour systolic pressure, mmHg†	116±11	43	119±11	0.008	121±13	19	123±76	0.311	122±11	33	124±15	0.073	118±11	95	121±13	<0.001
24-hour diastolic pressure, mmHg†	73±8	43	75±7	0.204	74±8	19	76±8	0.100	73±7	33	74±8	0.678	74±7	95	75±7	0.012
Hypertension, %	37	0	46	0.044	61	1	72	0.113	80	0	94	<0.001	53	1	69	<0.001
Metabolic variables																
BMI, kg/m^2	25.6±3.7	0	26.0±3.8	0.204	27.8±3.8	0	28.1±4.5	0.650	29.1±4.0	1	30.7±5.5	0.003	26.9±4.1	1	28.2±5.1	<0.001
Waist, cm	90.9±10.9	2	92.6±12.1	0.109	98.8±11.6	0	98.7±12.5	0.979	104.2±11.4	1	108.3±15.2	0.006	95.7±12.6	3	99.7±15.2	<0.001
Total cholesterol, mmol/L	5.59±1.00	3	5.52±1.09	0.449	5.47±1.11	0	5.50±1.28	0.871	4.49±0.92	1	4.38±1.12	0.336	5.28±1.11	4	5.08±1.26	0.007
High-density lipoprotein, mmol/L	1.53±0.48	3	1.40±0.35	0.001	1.39±0.37	0	1.33±0.43	0.324	1.18±0.31	1	1.09±0.35	0.015	1.41±0.45	4	1.27±0.39	<0.001
Low-density lipoprotein, mmol/L	3.54±0.88	3	3.57±0.98	0.681	3.39±1.00	0	3.42±1.09	0.885	2.54±0.79	1	2.49±0.98	0.636	3.25±0.98	4	3.13±1.12	0.079
Triglycerides, mmol/L	1.01 [0.76;1.41]	3	1.03 [0.79;1.48]	0.266	1.32 [0.90;1.79]	0	1.46 [1.06;2.19]	0.103	1.66 [1.17;2.09]	1	1.64 [1.16;2.40]	0.441	1.19 [0.85;1.75]	4	1.60 [0.92;1.94]	0.001
Total-to-HDL-cholesterol ratio	3.96±1.30	3	4.18±1.27	0.059	4.15±1.17	0	4.42±1.36	0.154	3.95±0.95	1	4.25±1.25	0.019	3.99±1.20	4	4.25±1.28	0.001
HbA1C, in %‡	5.5±0.3	3	5.6±0.4	0.068	5.9±0.4	1	5.8±0.4	0.166	6.8±1.0	0	7.1±1.1	0.006	5.9±0.8	4	6.2±1.0	<0.001
Fasting plasma glucose, mmol/L§	5.2±0.4	1	5.3±0.4	0.071	6.0±0.5	0	5.9±0.6	0.283	7.8±2.0	1	8.1±2.3	0.273	6.0±1.5	2	6.4±1.9	<0.001
Kidney function																
eGFR, ml/min 1.73m^2	91.0±13.9	12	90.6±13.7	0.771	85.5±14.1	1	85.4±14.1	0.967	86.3±16.3	7	81.8±18.7	0.023	88.8±14.8	20	86.3±16.4	0.012
Albuminuria, %	3.2	5	4.6	0.392	5.2	1	9.7	0.239	16.9	7	21.1	0.343	7.1	13	11.7	0.011
Lifestyle variables																
Smoking status: never/former/current, %	39.5/45.5/15.0	5	28.3/48.6/23.1	0.012	28.7/60.9/10.4	3	30.0/54.3/15.7	0.516	26.6/59.3/14.1	15	20.1/62.6/17.3	0.372	34.2/51.8/14.0	23	25.7/54.7/19.6	0.004
Alcohol use: no/low/high, %	13.2/55.0/31.8	8	14.1/49.4/36.5	0.466	13.0/50.4/36.5	3	12.9/61.4/25.7	0.282	28.2/46.9/24.9	14	32.9/50.7/16.4	0.182	17.1/52.1/30.8	25	20.8/52.1/27.1	0.234

Moderate to vigorous physical activity, hours/week[#]	5.4 [3.0;8.9]	69	5.5 [3.0;8.6]	0.822	4.5 [2.3;6.8]	25	3.0 [1.5;7.0]	0.087	3. [2.3;6.5]	74	3.0 [1.4;5.8]	0.048	4.6 [3.0;7.8]	168	4.5 [1.6;7.5]	0.007
Medication																
Anti-hypertensive medication, %	21	0	24	0.332	41	0	52	0.133	64	0	82	<0.001	36	0	54	<0.001
RAS inhibitors, %	14	0	16	0.466	31	0	32	0.977	51	0	69	0.001	27	0	39	<0.001
Beta- blockers, %	7	0	11	0.153	19	0	27	0.185	33	0	37	0.419	16	0	24	0.002
Diuretics, %	6	0	8	0.362	15	0	23	0.140	22	0	34	0.017	12	0	21	<0.001
Calcium antagonists, %	3	0	3	0.823	4	0	14	0.042	15	0	25	0.031	7	0	13	<0.001
Oral antidiabetics and/or insulin use	-	-	-	-	-	-	-	-	75	0	82	0.142	20	0	31	<0.001
Lipid-modifying medication, %	15	0	20	0.142	37	0	34	0.751	75	0	75	0.969	34	0	44	0.003
Mobility limitation, %[††]	12	13	16	0.280	27	6	28	0.913	31	25	50	0.001	30	44	20	<0.001
LA volume index, ml/m^2																
Total	30.2±6.5	86	31.3±8.1	0.191	30.0±7.0	33	30.2±6.7	0.859	29.4±6.9	66	30.9±8.4	0.134	30.0±6.7	185	30.9±7.9	0.112
Men	31.0±6.5	37	32.7±9.0	0.172	30.7±7.9	19	29.9±6.2	0.674	30.0±6.9	53	30.8±7.6	0.474	30.6±7.0	109	31.3±7.9	0.327
Women	29.6±6.4	49	29.7±6.6	0.918	29.0±5.2	14	30.6±7.7	0.441	28.2±6.9	13	31.0±9.5	0.151	29.3±6.3	76	30.3±7.9	0.241
LV mass index, gr/m$^{2.7}$																
Total	28.8±6.2	73	30.2±6.9	0.040	31.6±6.9	32	29.6±7.2	0.114	31.4±6.8	60	35.0±8.5	<0.001	29.9±6.6	165	32.0±8.0	<0.001
Men	29.9±6.8	34	32.1±7.3	0.048	31.7±6.8	19	30.3±6.3	0.386	31.5±7.2	48	35.5±8.1	0.001	30.8±7.0	101	33.3±7.7	0.001
Women	27.9±5.6	39	28.4±6.1	0.571	27.9±5.6	13	28.5±8.5	0.212	31.1±5.7	12	34.2±9.1	0.073	29.0±6.1	64	30.4±8.0	0.113
LV mass index, gr/m^2																
Total	65.0±13.8	73	68.3±15.2	0.034	68.8±14.1	32	64.3±14.0	0.082	67.0±14.7	60	71.0±16.0	0.042	66.2±14.2	165	68.7±15.4	0.022
Men	70.1±15.4	34	75.7±14.7	0.022	71.6±13.8	19	68.0±12.5	0.263	69.7±15.5	48	73.4±14.5	0.098	70.2±15.1	101	73.4±14.5	0.035
Women	61.2±11.2	39	61.2±12.0	0.992	64.8±13.6	13	58.5±14.7	0.147	61.4±10.9	12	66.3±17.0	0.132	61.8±11.6	64	62.5±14.4	0.586
Maximum tricuspid regurgitation flow, m/s	1.94±0.42	77	1.94±0.45	0.991	1.81±0.55	32	1.95±0.54	0.147	1.88±0.50	61	1.86±0.51	0.749	1.90±0.47	170	1.91±0.49	0.811
Cardiorespiratory fitness (W_{max})[§§]	168.5±49.0	85	158.7±44.7	0.078	166.5±47.3	42	167.4±56.3	0.931	156.7±42.6	101	160.4±52.8	0.602	165.1±47.3	228	160.7±49.2	0.281
Cardiorespiratory fitness adjusted for body mass (W_{max}/kg)[§§]	2.26±0.55	85	2.18±0.57	0.208	2.04±0.50	42	2.13±0.69	0.439	1.85±0.51	101	1.82±0.53	0.707	2.12±0.56	228	2.06±0.60	0.275

Data are presented as mean ± SD, median [interquartile-range] or frequencies (in %) as appropriate. Data present the two-dimensional echocardiography study population for regression models 1-3. Significant difference between the tissue Doppler imaging echocardiography study population and excluded individuals with missing values in models 1 to 3 was tested by independent t-test or chi-square test as appropriate. Abbreviations: BMI, body mass index, eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein; MINI, mini-international neuropsychiatric interview; NGM, normal glucose metabolism; PHQ, patient health questionnaire; T2D, type 2 diabetes.
[$]=The total number of missings in the study population is listed here. For the covariates included in regression models 1 to 3, the number of individuals available in the excluded group was 192/77/162/438 for respectively normal glucose metabolism, prediabetes, type 2 diabetes and the total study population, minus the number of missings in the study population. For the covariates not included in regression models 1 to 3, the number of individuals available in the study population and available in the excluded group are indicated with footnotes [*] to [§§] for respectively normal glucose metabolism, prediabetes, type 2 diabetes and the total study population. *=Educational level was available in 379/115/177/671 in the study population and 178/73/154/405 in the excluded group; **=Current atrial fibrillation or flutter was available in 364/107/171/642 in the study population and 170/70/147/426 in the excluded group; [†]=24-hour blood pressure measurements were available in 351/103/163/617 in the study population and 164/66/135/365 in the excluded group; [‡]=HbA1c was available in 379/114/177/670 in the study population and 176/73/153/403 in the excluded group; [§]=Fasting plasma glucose was available in 380/115/177/672 in the study population and 177/73/153/403 in the excluded group;; [#]Moderate to vigorous physical activity was available in 336/96/151/583 in the study population and in 153/67/106/326 in the excluded group; [††]=Mobility limitation was available in 378/114/176/668 in the study population and 167/68/130/365 in the excluded group; [§§]=93/31/53/177 were excluded due to missing on echocardiographic analyses or covariate.

Table S6. Interaction effects between measures of LV diastolic function and glucose metabolism status (NGM as reference) in the associations with cardiorespiratory fitness

		Prediabetes			Type 2 diabetes		
	Model	**B**	**95% CI**	**P**	**B**	**95% CI**	**P**
Average E/e'-ratio	**2**	0.022	(-0.021;0.065)	0.310	0.023	(-0.017;0.062)	0.258
e' average, cm/s	**2**	0.008	(-0.039;0.055)	0.731	-0.027	(-0.073;0.018)	0.239
Maximum tricuspid regurgitation flow, m/s	**2**	-0.152	(-0.341;0.037)	0.115	-0.070	(-0.245;0.105)	0.432
LA volume index, ml/m^2	**2**	-0.017	(-0.031;-0.003)	0.016	-0.011	(-0.023;0.001)	0.069
LV mass index, gr/m$^{2.7}$	**2**	-0.010	(-0.024;0.004)	0.179	-0.012	(-0.024;-0.012)	0.065
LV mass index, gr/m^2	**2**	-0.005	(-0.011;0.002)	0.179	-0.020	(-0.012;-0.001)	0.021
Diastolic function 2016 guidelines							
Indeterminate	**2**	-0.163	(-0.337;0.012)	0.131	-0.122	(-0.321;0.077)	0.230
Abnormal	**2**	-0.183	(-0.493;0.126)	0.246	-0.146	(-0.409;0.117)	0.277

N=672 or 639 for the two-dimensional or tissue Doppler imaging echocardiography study population, respectively. The unstandardized regression coefficients (B) represent the interaction effect between one unit higher level of measure of diastolic function (or for diastolic function according to 2016 guidelines versus normal diastolic function) and (pre)diabetes as compared to normal glucose metabolism, in the association with cardiorespiratory fitness in Wmax/kg. Model 2: adjusted for age, sex, height, prior cardiovascular disease, smoking status, alcohol use, total-to-HDL-cholesterol ratio, triglycerides, use of lipid-modifying medication, estimated glomerular filtration rate, health status, office systolic pressure, use of antihypertensive medication, albuminuria and interaction term between measure of diastolic function and glucose metabolism status.
Abbreviations: CI, confidence interval; LA, left atrial; LV, left ventricular.

Table S7. Associations between measures of LV diastolic function and cardiorespiratory fitness (Wmax/kg) in the total study population

		Total study population (N=672/639)		
Model		**B**	**95% CI**	**P**
Average E/e'-ratio	**1**	-0.048	(-0.066;-0.030)	<0.001
	2	-0.037	(-0.055;-0.018)	<0.001
	3	-0.025	(-0.043;-0.008)	0.005
e' average, cm/s	**1**	0.033	(-0.013;-0.054)	0.002
	2	0.013	(-0.008;0.035)	0.222
	3	0.007	(-0.013;0.027)	0.501
Maximum tricuspid regurgitation flow, m/s	**1**	0.103	(0.023;0.183)	0.011
	2	0.070	(-0.008;0.147)	0.080
	3	0.047	(-0.024;0.118)	0.194
LA volume index, ml/m^2	**1**	0.010	(0.005;0.016)	<0.001
	2	0.008	(0.003;0.014)	0.003
	3	0.007	(0.002;0.011)	0.009
LV mass index, gr/m$^{2.7}$	**1**	0.000	(-0.006;0.005)	0.894
	2	0.003	(-0.003;0.009)	0.291
	3	0.010	(0.004;0.015)	<0.001
Diastolic function 2016 guidelines				
Indeterminate	**1**	-0.056	(-0.142;0.030)	0.202
	2	-0.018	(-0.102;0.066)	0.676
	3	0.035	(-0.043;0.113)	0.378
Abnormal	**1**	0.022	(-0.099;0.144)	0.720
	2	0.073	(-0.046;0.192)	0.231
	3	0.093	(-0.018;0.203)	0.099

N=672 or 639 for the two-dimensional or tissue Doppler imaging echocardiography study population, respectively. The unstandardized regression coefficients (B) represent the difference in cardiorespiratory fitness in Wmax/kg per one unit higher level of measure of diastolic dysfunction, and for diastolic function according to 2016 guidelines versus normal diastolic function. Model 1: age, sex, height; Model 2: model 1 + prior cardiovascular disease, smoking status, alcohol use, total-to-HDL-cholesterol ratio, triglycerides, use of lipid-modifying medication, estimated glomerular filtration rate, health status, office systolic pressure, use of antihypertensive medication, albuminuria; model 3: model 2 + waist. Abbreviations: CI, confidence interval; LA, left atrial; LV, left ventricular.

Table S8. Associations between measures of LV diastolic function and cardiorespiratory fitness (Wmax/kg) – additional analyses with unindexed or other indexed measures of diastolic function

		Normal glucose metabolism (N=380)			Prediabetes (N=115)			Type 2 diabetes (N=177)		
Model		**B**	**95% CI**	**P**	**B**	**95% CI**	**P**	**B**	**95% CI**	**P**
LA volume index, ml/m²	**1**	0.017	(0.010;0.025)	<0.001	-0.003	(-0.015;0.010)	0.674	0.003	(-0.008;0.014)	0.516
	2	0.015	(0.008;0.022)	<0.001	-0.007	(-0.021;0.008)	0.357*	0.001	(-0.009;0.012)	0.804*
	3	0.014	(0.007;0.021)	<0.001	-0.006	(-0.018;0.007)	0.358	-0.002	(-0.011;0.007)	0.618
LA volume, ml	**1**	0.003	(-0.001;0.007)	0.088	-0.006	(-0.011;0.000)	0.057	-0.004	(-0.009;0.001)	0.158
	2	0.004	(0.000;0.008)	0.063	-0.007	(-0.014;-0.001)	0.026*	-0.004	(-0.009;0.001)	0.145*
	3	0.007	(0.010;0.010)	<0.001	-0.003	(-0.009;0.002)	0.247	-0.002	(-0.006;0.003)	0.412
LV mass index, gr/m$^{2.7}$	**1**	0.005	(-0.003;0.013)	0.224	-0.002	(-0.015;0.011)	0.722	-0.009	(-0.020;0.002)	0.097
	2	0.009	(0.001;0.017)	0.035	0.001	(-0.013;0.015)	0.857	-0.006	(-0.017;0.005)	0.259*
	3	0.015	(0.008;0.023)	<0.001	0.009	(-0.004;0.022)	0.166	0.001	(-0.009;0.010)	0.859
LV mass index, gr/m²	**1**	0.008	(0.005;0.012)	<0.001	0.004	(-0.002;0.011)	0.171	0.001	(-0.004;0.007)	0.567
	2	0.009	(0.005;0.012)	<0.001	0.006	(-0.001;0.013)	0.094	0.002	(-0.003;0.007)	0.416*
	3	0.008	(0.005;0.011)	<0.001	0.005	(-0.001;0.011)	0.128	0.001	(-0.003;0.006)	0.587
LV mass, gr	**1**	0.001	(0.000;0.003)	0.125	-0.001	(-0.004;0.002)	0.641	-0.002	(-0.004;0.000)	0.085
	2	0.002	(0.000;0.004)	0.016	0.000	(-0.003;0.004)	0.939*	-0.001	(-0.004;0.001)	0.236*
	3	0.004	(0.002;0.005)	<0.001	0.002	(-0.001;0.005)	0.222	0.000	(-0.002;0.002)	0.897

N=672 or 639 for the two-dimensional or tissue Doppler imaging echocardiography study population, respectively. The unstandardized regression coefficients (B) represent the difference in cardiorespiratory fitness in Wmax/kg per one unit higher level of measure of diastolic function. Model 1: age, sex, height; Model 2: model 1 + prior cardiovascular disease, smoking status, alcohol use, total-to-HDL-cholesterol ratio, triglycerides, use of lipid-modifying medication, estimated glomerular filtration rate, health status, office systolic pressure, use of antihypertensive medication, albuminuria; model 3: model 2 + waist.

Abbreviations: CI, confidence interval; LA, left atrial; LV, left ventricular.

*$P_{interaction}$<0.10, represents the P-value of the interaction effect between measures of diastolic function and (pre)diabetes as compared to normal glucose metabolism in the association with cardiorespiratory fitness.

Table S9. Associations between measures of LV diastolic function and cardiorespiratory fitness as % of predicted value Wmax

		Normal glucose metabolism (N=380/366)			Prediabetes (N=115/111)			Type 2 diabetes (N=177/162)		
	Model	**B**	**95% CI**	**P**	**B**	**95% CI**	**P**	**B**	**95% CI**	**P**
Average E/e'-ratio	**1**	-1.058	(-2.388;0.271)	0.118	-0.850	(-3.536;1.835)	0.532	-0.497	(-2.397;1.404)	0.607
	2	-1.337	(-2.743;0.069)	0.062	0.065	(-3.025;3.155)	0.967	-1.044	(-3.028;0.940)	0.300
	3	-1.513	(-2.923;-0.103)	0.035	-0.248	(-3.392;2.897)	0.876	-0.887	(-2.858;1.085)	0.375
e' average, cm/s	**1**	-0.428	(-1.751;0.895)	0.525	0.432	(-2.945;3.809)	0.800	-0.520	(-2.942;1.901)	0.672
	2	-0.137	(-1.600;1.327)	0.854	-0.564	(-4.620;3.492)	0.783	-0.485	(-3.085;2.116)	0.713
	3	-0.089	(-1.549;1.371)	0.905	-0.337	(-4.416;3.742)	0.870	-0.556	(-3.129;2.017)	0.670
Maximum tricuspid regurgitation flow, m/s	**1**	4.710	(-1.014;10.434)	0.107	-5.746	(-16.742;5.251)	0.303	-0.964	(-9.213;7.286)	0.818
	2	5.576	(-0.276;11.427)	0.062	-7.754	(-19.869;4.361)	0.207	-2.736	(-11.161;5.688)	0.522
	3	6.003	(0.183;11.823)	0.043	-7.679	(-19.878;4.521)	0.215	-2.732	(-11.116;5.652)	0.521
LA volume index, ml/m^2	**1**	0.556	(0.190;0.923)	0.003	-0.307	(-1.187;0.573)	0.491	-0.091	(-0.664;0.481)	0.753
	2	0.609	(0.230;0.989)	0.002	-0.465	(-1.454;0.524)	0.353*	-0.173	(-0.753;0.407)	0.556
	3	0.629	(0.253;1.006)	0.001	-0.468	(-1.462;0.526)	0.352	-0.224	(-0.803;0.356)	0.447
LV mass index, gr/m$^{2.7}$	**1**	0.907	(0.525;1.288)	<0.001	0.526	(-0.369;1.420)	0.247	-0.017	(-0.585;0.551)	0.952
	2	0.993	(0.599;1.386)	<0.001	1.012	(0.038;1.986)	0.042*	0.026	(-0.576;0.627)	0.933*
	3	0.932	(0.529;1.334)	<0.001	1.031	(0.027;2.034)	0.044	0.125	(-0.485;0.735)	0.686
Diastolic function 2016 guidelines										
Indeterminate	**1**	5.555	(0.164;10.947)	0.043	2.853	(-12.072;17.779)	0.705	-3.819	(-13.840;6.203)	0.453
	2	5.056	(-0.469;10.582)	0.073	-1.388	(-17.184;14.408)	0.862	-3.372	(-13.738;6.994)	0.521
	3	4.480	(-1.074;10.033)	0.114	-2.827	(-18.814;13.161)	0.726	-2.430	(-12.725;7.865)	0.641
Abnormal	**1**	10.191	(1.879;18.504)	0.016	3.278	(-16.501;23.057)	0.743	-7.991	(-20.689;4.706)	0.216
	2	10.763	(2.292;19.234)	0.013	5.380	(-15.103;25.864)	0.603	-7.676	(-20.698;5.345)	0.246*
	3	10.604	(2.152;19.056)	0.014	4.706	(-15.790;25.203)	0.649	-7.504	(-20.387;5.378)	0.251

N=672 or 639 for the two-dimensional or tissue Doppler imaging echocardiography study population, respectively. The unstandardized regression coefficients (B) represent the difference in cardiorespiratory fitness in Wmax/kg per one unit higher level of measure of diastolic function, and for diastolic function according to 2016 guidelines versus normal diastolic function. Model 1: age, sex, height; Model 2: model 1 + prior cardiovascular disease, smoking status, alcohol use, total-to-HDL-cholesterol ratio, triglycerides, use of lipid-modifying medication, estimated glomerular filtration rate, health status, office systolic pressure, use of antihypertensive medication, albuminuria; model 3: model 2 + waist.
Abbreviations: CI, confidence interval; LA, left atrial; LV, left ventricular.
*$P_{interaction}$<0.04, represents the P-value of the interaction effect between measures of diastolic function and (pre)diabetes as compared to normal glucose metabolism in the association with cardiorespiratory fitness.

Table S10. Additional analyses in the associations between measures of LV diastolic function and cardiorespiratory fitness

		Normal glucose metabolism (N=380/366)			Prediabetes (N=115/111)			Type 2 diabetes (N=177/162)		
	Model	**B**	**95% CI**	**P**	**B**	**95% CI**	**P**	**B**	**95% CI**	**P**
Average E/e'-ratio	**2**	**-0.044**	**(-0.071;-0.016)**	**0.002**	**-0.030**	**(-0.072;0.012)**	**0.156**	**-0.037**	**(-0.072;-0.001)**	**0.043**
	2a	-0.039	(-0.067;-0.010)	0.008	-0.025	(-0.070;0.020)	0.280	-0.032	(-0.071;0.006)	0.101
	2b	-0.045	(-0.075;-0.016)	0.003	-0.033	(-0.076;0.010)	0.135	-0.048	(-0.087;-0.009)	0.015
	2c	-0.042	(-0.070;-0.014)	0.003	-0.028	(-0.070;0.014)	0.185	-0.038	(-0.074;-0.001)	0.041
	2d	-0.044	(-0.072;-0.016)	0.002	-0.033	(-0.074;0.009)	0.120	-0.035	(-0.072;0.002)	0.063
	2e	-0.037	(-0.066;-0.008)	0.012	-0.026	(-0.070;0.018)	0.242	-0.034	(-0.069;0.001)	0.059
	2f	-0.046	(-0.076;-0.017)	0.002	-0.036	(-0.099;0.026)	0.251	-0.023	(-0.062;0.016)	0.246
	2g	-0.044	(-0.071;-0.016)	0.002	-0.036	(-0.077;0.005)	0.086	-0.035	(-0.070;0.000)	0.047
	2h	-0.049	(-0.079;-0.023)	0.001	-0.038	(-0.078;0.003)	0.066	-0.036	(-0.071;-0.001)	0.041
	2i	-0.051	(-0.080;-0.025)	<0.001	-0.029	(-0.075;0.017)	0.218	-0.034	(-0.071;0.004)	0.077
	2j	-0.049	(-0.077;-0.021)	<0.001	-0.028	(-0.073;0.018)	0.230	-0.032	(-0.069;0.005)	0.088
	2k	-0.044	(-0.071;-0.017)	0.002	-0.031	(-0.073;0.011)	0.148	-0.037	(-0.073;-0.001)	0.042
	2l	-0.044	(-0.072;-0.016)	0.002	-0.028	(-0.070;0.015)	0.202	-0.037	(-0.073;-0.002)	0.041
	3	**-0.033**	**(-0.060;-0.007)**	**0.014**	**-0.015**	**(-0.055;0.025)**	**0.450**	**-0.028**	**(-0.059;0.003)**	**0.077**
	3a	-0.029	(-0.055;-0.002)	0.033	-0.016	(-0.056;0.023)	0.409	-0.023	(-0.054;0.009)	0.156
	3b	-0.029	(-0.055;-0.002)	0.035	-0.017	(-0.056;0.022)	0.394	-0.020	(-0.052;0.011)	0.207
e' average cm/s	**2**	**0.013**	**(-0.016;0.042)**	**0.388**	**0.040**	**(-0.016;0.095)**	**0.158**	**-0.010**	**(-0.057;0.037)**	**0.662**
	2a	0.014	(-0.016;0.044)	0.347	0.038	(-0.026;0.101)	0.240	-0.020	(-0.068;0.027)	0.403
	2b	0.014	(-0.016;0.044)	0.357	0.036	(-0.021;0.092)	0.217	-0.003	(-0.055;0.049)	0.914
	2c	0.010	(-0.019;0.040)	0.492	0.021	(-0.038;0.080)	0.483	-0.004	(-0.053;0.045)	0.878
	2d	0.013	(-0.016;0.042)	0.385	0.034	(-0.021;0.089)	0.227	-0.014	(-0.062;0.033)	0.551
	2e	0.009	(-0.021;0.039)	0.546	0.039	(-0.017;0.096)	0.172	-0.010	(-0.058;0.037)	0.664
	2f	0.019	(-0.012;0.050)	0.233	0.071	(-0.006;0.137)	0.033	-0.023	(-0.077;0.032)	0.413
	2g	0.012	(-0.018;0.041)	0.430	0.039	(-0.017;0.095)	0.168	-0.013	(-0.060;0.034)	0.585
	2h	0.018	(-0.011;0.047)	0.217	0.049	(-0.005;0.102)	0.073	-0.009	(-0.055;0.038)	0.714
	2i	0.027	(-0.002;0.057)	0.066	0.030	(-0.025;0.085)	0.286	-0.008	(-0.057;0.041)	0.748
	2j	0.025	(-0.005;0.054)	0.098	0.030	(-0.025;0.086)	0.282	-0.009	(-0.058;0.040)	0.717

	2k	0.013	(-0.016;0.042)	0.381	0.041	(-0.014;0.096)	0.146	-0.009	(-0.057;0.038)	0.697
	2l	0.015	(-0.014;0.024)	0.318	0.040	(-0.015;0.096)	0.149	-0.010	(-0.057;0.038)	0.688
	3	**0.009**	**(-0.018;0.037)**	**0.501**	**0.028**	**(-0.023;0.079)**	**0.280**	**-0.014**	**(-0.055;0.026)**	**0.487**
	3a	0.007	(-0.021;0.034)	0.622	0.035	(-0.016;0.086)	0.174	-0.014	(-0.055;0.027)	0.508
	3b	0.007	(-0.020;0.034)	0.622	0.033	(-0.017;0.084)	0.196	-0.015	(-0.056;0.025)	0.453
Maximum tricuspid regurgitation flow, m/s	**2**	**0.137**	**(0.023;0.252)**	**0.019**	**-0.054**	**(-0.213;0.134)**	**0.653**	**-0.021**	**(-0.175;0.133)**	**0.785**
	2a	0.141	(0.023;0.259)	0.020	0.044	(-0.146;0.235)	0.645	-0.139	(-0.305;0.027)	0.101
	2b	0.132	(0.016;0.249)	0.026	-0.059	(-0.238;0.119)	0.513	-0.026	(-0.189;0.138)	0.758
	2c	0.134	(0.019;0.249)	0.022	-0.077	(-0.252;0.097)	0.382	-0.023	(-0.184;0.138)	0.779
	2d	0.138	(0.023;0.253)	0.019	-0.060	(-0.235;0.115)	0.499	-0.023	(-0.180;0.134)	0.772
	2e	0.146	(0.028;0.265)	0.016	-0.017	(-0.192;0.158)	0.847	0.019	(-0.139;0.177)	0.809
	2f	0.209	(0.084;0.335)	0.001	-0.069	(-0.298;0.161)	0.552	-0.016	(-0.200;0.168)	0.865
	2g	0.142	(0.027;0.256)	0.016	-0.028	(-0.198;0.143)	0.749	-0.025	(-0.179;0.129)	0.746
	2h	0.129	(0.015;0.243)	0.027	-0.023	(-0.198;0.151)	0.791	-0.022	(-0.175;0.131)	0.776
	2i	0.142	(0.021;0.262)	0.022	-0.042	(-0.233;0.149)	0.664	-0.027	(-0.189;0.134)	0.738
	2j	0.142	(0.021;0.262)	0.021	-0.040	(-0.229;0.149)	0.677	-0.023	(-0.184;0.137)	0.774
	2k	0.141	(0.027;0.255)	0.016	-0.062	(-0.235;0.110)	0.475	-0.024	(-0.181;0.132)	0.761
	2l	0.137	(0.022;0.252)	0.019	-0.040	(-0.216;0.135)	0.648	-0.022	(-0.176;0.133)	0.784
	3	**0.114**	**(0.007;0.222)**	**0.037**	**-0.064**	**(-0.218;0.090)**	**0.411**	**-0.021**	**(-0.153;0.111)**	**0.754**
	3a	0.108	(0.001;0.216)	0.048	-0.044	(-0.198;0.111)	0.578	-0.021	(-0.154;0.112)	0.758
	3b	0.107	(0.000;0.214)	0.051	-0.048	(-0.202;0.107)	0.542	-0.024	(-0.156;0.107)	0.718

N=672, 380/115/177 or 639, 366/111/162 for the two-dimensional or tissue Doppler imaging echocardiography study population, respectively. The unstandardized regression coefficients (B) respresent the difference in cardiorespiratory fitness in Wmax/kg per one unit higher level of measure of diastolic function, and for diastolic function according to 2016 guidelines versus normal diastolic function. Model 1: age, sex, height; Model 2: model 1 + prior cardiovascular disease, smoking status, alcohol use, total-to-HDL-cholesterol ratio, triglycerides, use of lipid-modifying medication, estimated glomerular filtration rate, health status, office systolic blood pressure, use of antihypertensive medication, albuminuria; Model 2a: additional adjustment for moderate to vigorous physical activity (N=336/96/151 or N=322/94/138); Model 2b: exclusion of individuals with prior coronary heart disease (N=368/96/151 or N=355/104/148); Model 2c: exclusion of individuals with atrial fibrillation)N=364/107/169 or N=350/103/155); Model 2d: exclusion of individuals with wall abnormalities (N=377/114/173 or N=365/110/159); Model 2e: exclusion of individuals with valvular dysfunction (N=356/108/168 or N=343/104/154); Model 2f: exclusion of individuals with mobility limitations (N=332/83/122 or N=320/82/114); Model 2g: replacement of office systolic pressure with office diastolic pressure; Model 2h: replacement of office systolic pressure and antihypertensive medication with presence of hypertension; Model 2i: replacement of office systolic pressure with 24-hour systolic pressure (N=351/103/163 or N=340/101/149); Model 2j: replacement of office systolic pressure with 24-hour diastolic pressure (N=351/103/163 or N=340/101/149); Model 2k: additional adjustment for renin-angiotensin-system-inhibitors; Model 2l: additional adjustment for beta-blockers; Model 3: model 2 + waist; Model 3a: replacement of waist with body mass index; Model 3b replacement of waist with weight.

Abbreviations: CI, confidence interval; LA, left atrial; LV, left ventricular.

Table S11. Additional analyses in the associations between measures of LV diastolic function and cardiorespiratory fitness

		Normal glucose metabolism (N=380/366)			Prediabetes (N=115/111)			Type 2 diabetes (N=177/162)		
	Model	**B**	**95% CI**	**P**	**B**	**95% CI**	**P**	**B**	**95% CI**	**P**
LA volume index, ml/m^2	**2**	**0.015**	**(0.008;0.022)**	**<0.001**	**-0.007**	**(-0.021;0.008)**	**0.357**	**0.001**	**(-0.009;0.012)**	**0.804**
	2a	0.014	(0.006;0.022)	<0.001	0.008	(-0.010;0.025)	0.327	-0.002	(-0.014;0.009)	0.662
	2b	0.015	(0.008;0.023)	<0.001	-0.004	(-0.019;0.010)	0.580	0.000	(-0.011;0.012)	0.935
	2c	0.014	(0.007;0.022)	<0.001	-0.006	(-0.021;0.008)	0.384	0.005	(-0.007;0.017)	0.432
	2d	0.015	(0.007;0.022)	<0.001	-0.006	(-0.020;0.009)	0.434	0.003	(-0.008;0.014)	0.580
	2e	0.016	(0.008;0.024)	<0.001	0.000	(-0.016;0.016)	0.982	0.005	(-0.007;0.018)	0.398
	2f	0.016	(0.008;0.023)	<0.001	-0.011	(-0.027;0.006)	0.206	-0.002	(-0.014;0.010)	0.726
	2g	0.014	(0.006;0.021)	<0.001	-0.009	(-0.023;0.005)	0.220	0.001	(-0.010;0.011)	0.881
	2h	0.014	(0.007;0.022)	<0.001	-0.005	(-0.019;0.009)	0.467	0.002	(-0.009;0.012)	0.757
	2i	0.015	(0.007;0.022)	<0.001	-0.001	(-0.015;0.014)	0.901	0.000	(-0.011;0.011)	0.968
	2j	0.015	(0.007;0.023)	<0.001	-0.001	(-0.016;0.013)	0.896	0.000	(-0.011;0.011)	0.988
	2k	0.014	(0.007;0.022)	<0.001	-0.008	(-0.022;0.006)	0.273	0.001	(-0.010;0.012)	0.822
	2l	0.015	(0.007;0.022)	<0.001	-0.007	(-0.021;0.008)	0.361	0.001	(-0.009;0.012)	0.808
	3	**0.014**	**(0.007;0.021)**	**<0.001**	**-0.006**	**(-0.018;0.007)**	**0.358**	**-0.002**	**(-0.011;0.007)**	**0.618**
	3a	0.014	(0.007;0.021)	<0.001	-0.004	(-0.017;0.008)	0.485	0.001	(-0.008;0.010)	0.818
	3b	0.014	(0.007;0.021)	<0.001	-0.005	(-0.017;0.008)	0.476	0.001	(-0.008;0.010)	0.890
LV mass index, gr/m$^{2.7}$	**2**	**0.009**	**(0.001;0.017)**	**0.035**	**0.001**	**(-0.013;0.015)**	**0.857**	**-0.006**	**(-0.017;0.005)**	**0.259**
	2a	0.009	(0.001;0.017)	0.035	0.010	(-0.005;0.024)	0.201	-0.005	(-0.018;0.008)	0.463
	2b	0.009	(0.001;0.017)	0.032	0.003	(-0.012;0.017)	0.728	-0.008	(-0.019;0.004)	0.184
	2c	0.008	(0.000;0.017)	0.042	0.006	(-0.009;0.020)	0.439	-0.007	(-0.019;0.004)	0.210
	2d	0.009	(0.001;0.017)	0.033	0.003	(-0.012;0.017)	0.724	-0.007	(-0.019;0.004)	0.210
	2e	0.009	(0.001;0.018)	0.025	0.004	(-0.012;0.019)	0.652	-0.008	(-0.019;0.004)	0.187
	2f	0.010	(0.002;0.019)	0.021	0.001	(-0.016;0.018)	0.904	-0.004	(-0.016;0.008)	0.469
	2g	0.008	(0.000;0.016)	0.038	0.001	(-0.013;0.015)	0.905	-0.006	(-0.017;0.004)	0.246
	2h	0.007	(-0.001;0.015)	0.079	-0.001	(-0.015;0.014)	0.939	-0.007	(-0.018;0.004)	0.197
	2i	0.006	(-0.002;0.014)	0.141	0.005	(-0.010;0.020)	0.490	-0.006	(-0.019;0.006)	0.286
	2j	0.006	(-0.002;0.014)	0.125	0.005	(-0.010;0.019)	0.532	-0.007	(-0.018;0.005)	0.256

2k	0.008	(0.000;0.016)	0.052	0.001	(-0.013;0.015)	0.872	-0.006	(-0.017;0.005)	0.265
2l	0.009	(0.001;0.016)	0.035	0.001	(-0.013;0.016)	0.850	-0.006	(-0.017;0.005)	0.262
3	**0.015**	**(0.008;0.023)**	**<0.001**	**0.009**	**(-0.004;0.022)**	**0.166**	**0.001**	**(-0.009;0.010)**	**0.859**
3a	0.018	(0.010;0.025)	<0.001	0.011	(-0.002;0.024)	0.095	0.003	(-0.007;0.013)	0.520
3b	0.018	(0.011;0.026)	<0.001	0.011	(-0.002;0.024)	0.095	0.003	(-0.006;0.013)	0.498

N=672, 380/115/177 or 639, 366/111/162 for the two-dimensional or tissue Doppler imaging echocardiography study population, respectively. The unstandardized regression coefficients (B) represent the difference in cardiorespiratory fitness in Wmax/kg per one unit higher level of measure of diastolic function, and for diastolic function according to 2016 guidelines versus normal diastolic function. Model 1: age, sex, height; Model 2: model 1 + prior cardiovascular disease, smoking status, alcohol use, total-to-HDL-cholesterol ratio, triglycerides, use of lipid-modifying medication, estimated glomerular filtration rate, health status, office systolic blood pressure, use of antihypertensive medication, albuminuria; Model 2a: additional adjustment for moderate to vigorous physical activity (N=336/96/151 or N=322/94/138); Model 2b: exclusion of individuals with prior coronary heart disease (N=368/96/151 or N=355/104/148); Model 2c: exclusion of individuals with atrial fibrillation)N=364/107/169 or N=350/103/155); Model 2d: exclusion of individuals with wall abnormalities (N=377/114/173 or N=365/110/159); Model 2e: exclusion of individuals with valvular dysfunction (N=356/108/168 or N=343/104/154); Model 2f: exclusion of individuals with mobility limitations (N=332/83/122 or N=320/82/114); Model 2g: replacement of office systolic pressure with office diastolic pressure; Model 2h: replacement of office systolic pressure and antihypertensive medication with presence of hypertension; Model 2i: replacement of office systolic pressure with 24-hour systolic pressure (N=351/103/163 or N=340/101/149); Model 2j: replacement of office systolic pressure with 24-hour diastolic pressure (N=351/103/163 or N=340/101/149); Model 2k: additional adjustment for renin-angiotensin-system-inhibitors; Model 2l: additional adjustment for beta-blockers; Model 3: model 2 + waist; Model 3a: replacement of waist with body mass index; Model 3b replacement of waist with weight.

Abbreviations: CI, confidence interval; LA, left atrial; LV, left ventricular.

Table S12. Additional analyses in the associations between measures of LV diastolic function and cardiorespiratory fitness

		Normal glucose metabolism (N=380/366)			Prediabetes (N=115/111)			Type 2 diabetes (N=177/162)		
	Model	**B**	**95% CI**	**P**	**B**	**95% CI**	**P**	**B**	**95% CI**	**P**
Diastolic function 2016 guidelines										
Indeterminate	**2**	**0.050**	**(-0.061;0.160)**	**0.374**	**-0.208**	**(-0.422;0.005)**	**0.055**	**-0.115**	**(-0.302;0.073)**	**0.229**
	2a	0.068	(-0.047;0.183)	0.244	-0.208	(-0.430;0.014)	0.066	-0.073	(-0.262;0.117)	0.450
	2b	0.062	(-0.051;0.175)	0.282	-0.223	(-0.443;-0.004)	0.046	-0.089	(-0.290;0.111)	0.381
	2c	0.055	(-0.058;0.168)	0.340	-0.141	(-0.357;0.075)	0.199	-0.105	(-0.297;0.086)	0.279
	2d	0.050	(-0.061;0.160)	0.378	-0.203	(-0.412;0.007)	0.058	-0.076	(-0.267;0.115)	0.433
	2e	0.056	(-0.055;0.168)	0.319	-0.238	(-0.457;-0.019)	0.034	-0.183	(-0.386;0.020)	0.077
	2f	0.047	(-0.070;0.165)	0.429	-0.451	(-0.712;-0.189)	0.001	-0.059	(-0.273;0.155)	0.586
	2g	0.044	(-0.065;0.154)	0.429	-0.213	(-0.426;0.000)	0.050	-0.109	(-0.297;0.079)	0.252
	2h	0.033	(-0.077;0.143)	0.550	-0.192	(-0.407;0.022)	0.078	-0.119	(-0.305;0.067)	0.208
	2i	0.021	(-0.093;0.135)	0.718	-0.240	(-0.466;-0.014))	0.038	-0.119	(-0.309;0.072)	0.219
	2j	0.028	(-0.085;0.142)	0.624	-0.239	(-0.466;0.013)	0.039	-0.120	(-0.309;0.069)	0.211
	2k	0.043	(-0.068;0.153)	0.447	-0.210	(-0.422;0.003)	0.054	-0.118	(-0.307;0.071)	0.218
	2l	0.048	(-0.062;0.159)	0.390	-0.219	(-0.433;-0.005)	0.045	-0.113	(-0.302;0.075)	0.237
	3	**0.095**	**(-0.009;0.199)**	**0.074**	**-0.144**	**(-0.345;0.057)**	**0.157**	**-0.064**	**(-0.227;0.100)**	**0.441**
	3a	0.093	(-0.011;0.197)	0.080	-0.155	(-0.353;0.043)	0.123	-0.075	(-0.240;0.090)	0.369
	3b	0.093	(-0.011;0.196)	0.080	-0.144	(-0.342;0.054)	0.151	-0.071	(-0.234;0.093)	0.393
Abnormal	**2**	**0.165**	**(-0.004;0.335)**	**0.055**	**-0.053**	**(-0.329;0.224)**	**0.706**	**-0.065**	**(-0.301;0.170)**	**0.229**
	2a	0.188	(0.009;0.368)	0.040	0.088	(-0.214;0.389)	0.563	-0.041	(-0.307;0.225)	0.763
	2b	0.169	(-0.004;0.343)	0.056	0.015	(-0.265;0.296)	0.914	-0.027	(-0.280;0.226)	0.835
	2c	0.167	(-0.005;0.340)	0.057	0.044	(-0.238;0.327)	0.756	-0.044	(-0.284;0.197)	0.722
	2d	0.166	(-0.004;0.335)	0.056	-0.008	(-0.283;0.267)	0.953	-0.028	(-0.267;0.211)	0.815
	2e	0.207	(0.025;0.390)	0.026	-0.028	(-0.307;0.251)	0.843	-0.004	(-0.260;0.252)	0.974
	2f	0.184	(0.006;0.362)	0.042	-0.262	(-0.608;0.084)	0.135	0.052	(-0.206;0.309)	0.692
	2g	0.160	(-0.009;0.328)	0.063	-0.062	(-0.340;0.215)	0.657	-0.070	(-0.305;0.164)	0.554
	2h	0.145	(-0.025;0.316)	0.095	-0.060	(-0.338;0.219)	0.672	-0.064	(-0.298;0.171)	0.592
	2i	0.086	(-0.092;0.135)	0.718	0.018	(-0.264;0.300)	0.985	-0.102	(-0.343;0.140)	0.406

2j	0.102	(-0.074;0.279)	0.255	-0.018	(-0.266;0.301)	0.902	-0.104	(-0.346;0.138)	0.398
2k	0.144	(-0.026;0.314)	0.097	-0.067	(-0.344;0.210)	0.633	-0.064	(-0.301;0.172)	0.591
2l	0.163	(-0.007;0.332)	0.060	-0.076	(-0.355;0.203)	0.588	-0.066	(-0.302;0.171)	0.583
3	**0.178**	**(0.019;0.337)**	**0.028**	**-0.022**	**(-0.280;0.235)**	**0.862**	**-0.056**	**(-0.260;0.149)**	**0.590**
3a	0.189	(-0.031;0.348)	0.020	-0.007	(-0.262;0.248)	0.956	-0.040	(-0.246;0.167)	0.703
3b	0.189	(0.031;0.347)	0.019	-0.001	(-0.255;0.254)	0.996	-0.045	(-0.249;0.160)	0.393

N=672, 380/115/177 or 639, 366/111/162 for the two-dimensional or tissue Doppler imaging echocardiography study population, respectively. The unstandardized regression coefficients (B) respresent the difference in cardiorespiratory fitness in Wmax/kg per one unit higher level of measure of diastolic function, and for diastolic function according to 2016 guidelines versus normal diastolic function. Model 1: age, sex, height; Model 2: model 1 + prior cardiovascular disease, smoking status, alcohol use, total-to-HDL-cholesterol ratio, triglycerides, use of lipid-modifying medication, estimated glomerular filtration rate, health status, office systolic blood pressure, use of antihypertensive medication, albuminuria; Model 2a: additional adjustment for moderate to vigorous physical activity (N=336/96/151 or N=322/94/138); Model 2b: exclusion of individuals with prior coronary heart disease (N=368/96/151 or N=355/104/148); Model 2c: exclusion of individuals with atrial fibrillation (N=364/107/169 or N=350/103/155); Model 2d: exclusion of individuals with wall abnormalities (N=377/114/173 or N=365/110/159); Model 2e: exclusion of individuals with valvular dysfunction (N=356/108/168 or N=343/104/154); Model 2f: exclusion of individuals with mobility limitations (N=332/83/122 or N=320/82/114); Model 2g: replacement of office systolic pressure with office diastolic pressure; Model 2h: replacement of office systolic pressure and antihypertensive medication with presence of hypertension; Model 2i: replacement of office systolic pressure with 24-hour systolic pressure (N=351/103/163 or N=340/101/149); Model 2j: replacement of office systolic pressure with 24-hour diastolic pressure (N=351/103/163 or N=340/101/149); Model 2k: additional adjustment for renin-angiotensin-system-inhibitors; Model 2l: additional adjustment for beta-blockers; Model 3: model 2 + waist; Model 3a: replacement of waist with body mass index; Model 3b replacement of waist with weight.

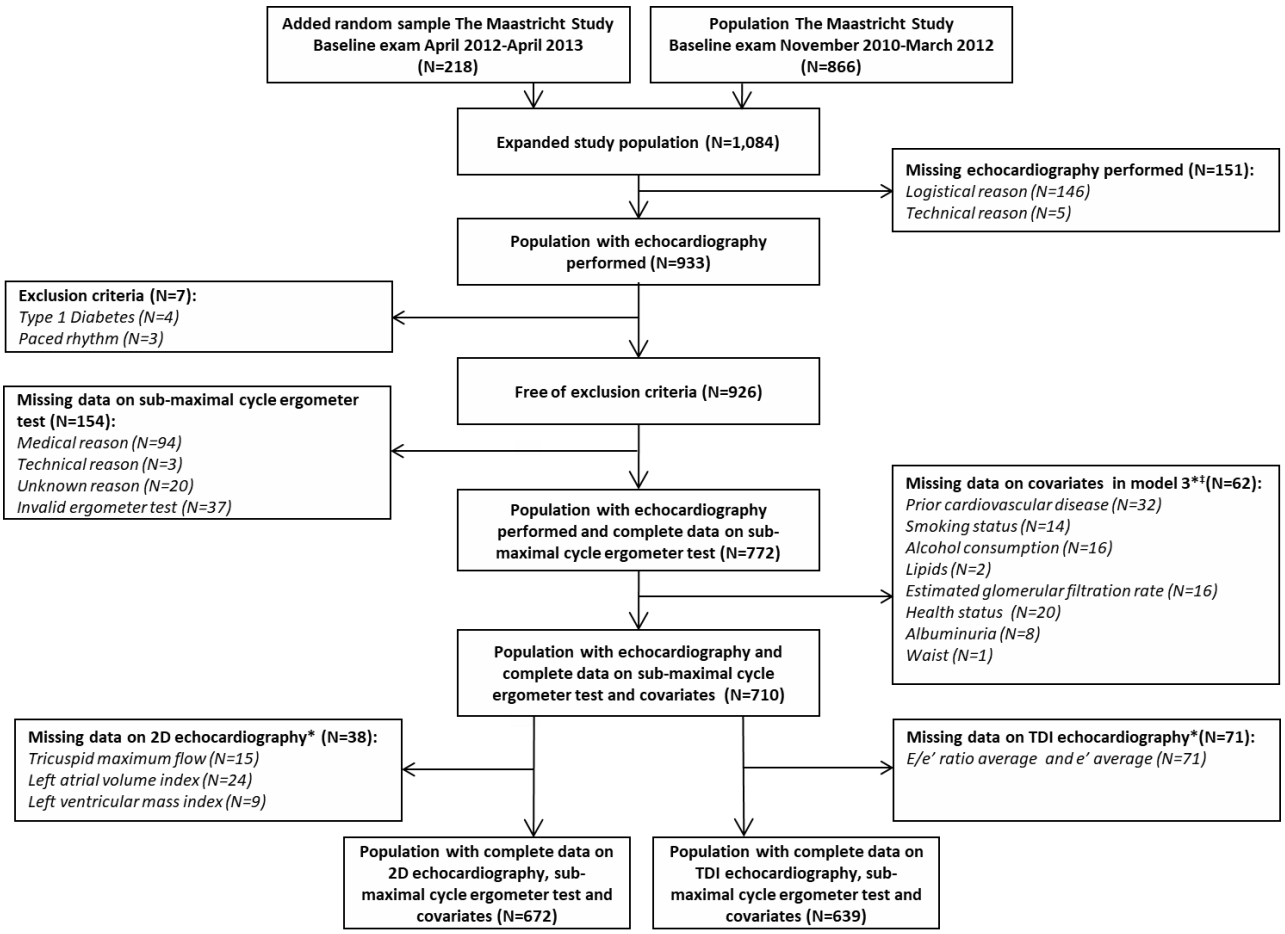
Abbreviations: CI, confidence interval; LA, left atrial; LV, left ventricular.

Table S13. Interaction effects between measures of diastolic function and sex in the associations with cardiorespiratory fitness

	Model	B	95% CI	P
Average E/e'-ratio	**2**	0.021	(-0.013;0.055)	0.219
e' average, cm/s	**2**	-0.020	(-0.055;0.014)	0.250
Maximum tricuspid regurgitation flow, m/s	**2**	-0.046	(-0.202;0.109)	0.558
LA volume index, ml/m^2	**2**	0.002	(-0.009;0.013)	0.715
LV mass index, gr/m$^{2.7}$	**2**	-0.008	(-0.019;0.003)	0.175

N=672 or 639 for the two-dimensional or tissue Doppler imaging echocardiography study population, respectively. The unstandardized regression coefficients (B) represent the interaction effect between one unit higher level of measure of diastolic function (or for diastolic function according to 2016 guidelines versus normal diastolic function) and (pre)diabetes as compared to normal glucose metabolism, in the association with cardiorespiratory fitness in Wmax/kg. Model 2: adjusted for age, sex, height, prior cardiovascular disease, smoking status, alcohol use, total-to-HDL-cholesterol ratio, triglycerides, use of lipid-modifying medication, estimated glomerular filtration rate, health status, office systolic pressure, use of antihypertensive medication, albuminuria, interaction term between measure of diastolic function and glucose metabolism status, and interaction term between measure of diastolic function and sex.
Abbreviations: CI, confidence interval; LA, left atrial; LV, left ventricular.

Figure S1. Two-dimensional and tissue Doppler imaging echocardiography study population selection.



*Categories of missing data were not mutually exclusive. No data was missing for the covariates sex, age and glucose metabolism status. ‡After selection of the population with echocardiography performed and complete data on the sub-maximal cycle ergometer test no additional data was missing for the covariates height, lipid-modifying medication, office systolic blood pressure, and antihypertensive medication