


# Consumption of animal and plant foods and risk of left ventricular diastolic dysfunction: the Bogalusa Heart Study

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## Abstract

**Aims** Left ventricular diastolic dysfunction (LVDD) is an early heart failure with preserved ejection fraction (HFpEF) phenotype that is reversible. Identifying dietary predictors associated with LVDD in diverse populations may help broadly improve HFpEF primary prevention.

**Methods and results** This longitudinal analysis included 456 individuals of the Bogalusa Heart Study (27% Black, 63% women, baseline age = 36.1 ± 4.4 years). Diet was measured at baseline through food frequency questionnaires. LVDD was defined at follow-up (median = 12.9 years) through echocardiographic measurement of the E/A ratio, E/e' ratio, isovolumic relaxation time, and deceleration time. Multivariable-adjusted logistic regression estimated the risk of LVDD according to dietary predictor, adjusting for traditional cardiovascular disease risk factors. Compared with the lowest tertile, participants in the middle tertile of total protein (OR = 3.30, 95% CI: 1.46, 7.45) and animal protein (OR = 2.91, 95% CI: 1.34, 6.34) consumption experienced the highest risk of LVDD. There was a 77% and 56% lower risk of LVDD for persons in the middle vs. lowest tertile of vegetable (OR = 0.23, 95% CI: 0.11, 0.49) and legume consumption (OR = 0.44, 95% CI: 0.22, 0.85), respectively. Total protein, animal protein, processed meat, and egg consumption indicated a quadratic trend towards increased risk of LVDD, while legume and vegetable intake conferred a quadratic trend towards decreased risk of LVDD (all quadratic  $P < 0.05$ ).

**Conclusions** Diets higher in animal foods and lower in plant foods are associated with an increased risk for LVDD. These findings suggest threshold effects of diet on LVDD, past which more traditional cardiometabolic determinants occupy a larger role in HFpEF risk.

**Keywords** Diastole; Plant-based diet; Red meat; Dietary protein; Heart failure; Cardiovascular diseases

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## Introduction

Heart failure (HF) is the most rapidly increasing form of cardiovascular disease globally.<sup>1,2</sup> In the United States, the prevalence of HF is projected to increase by nearly 50% over the next decade, affecting more than 8 million individuals by 2030.<sup>3</sup> Epidemiologic studies indicate that HF with preserved ejection fraction (HFpEF) is becoming the predominant form

of disease.<sup>4</sup> Given the dearth of therapeutic strategies for HFpEF,<sup>5</sup> identification and minimization of risk factors associated with subclinical HFpEF phenotypes is a novel approach to reverse the HF epidemic and reduce the societal and economic costs associated with this disease.

Left ventricular diastolic dysfunction (LVDD), characterized by impaired relaxation and elevated filling pressures, is one of the earliest insults on the myocardial ischaemic cascade and a

primary subclinical HFpEF phenotype.<sup>6,7</sup> In addition to sharing an independent association with all-cause mortality,<sup>8</sup> LVDD represents an important transitional point on the causal HFpEF pathway as previous research suggests that LVDD is reversible.<sup>9,10</sup> Preservation of diastolic function through dietary modification, in particular, may represent an efficient strategy to broadly improve primary prevention of HFpEF in the general population. Previous studies have shown that long-term calorie restriction<sup>11</sup> and modulation of carbohydrate intake<sup>12</sup> can improve diastolic function in healthy middle-aged individuals and HFpEF patients, respectively.

Dietary patterns with liberal whole grain, legume, fruit, and vegetable intake, including the Mediterranean<sup>13</sup> and Dietary Approaches to Stop Hypertension diets,<sup>14</sup> vs. a Southern or Western dietary pattern,<sup>15,16</sup> high in fried foods, processed meats, and added fat, have been associated with a lower and higher risk of incident HF, respectively. Despite these observations, it is unknown as to which isolated components of these dietary patterns may contribute to LVDD and future HFpEF risk. Likewise, while clinical trials have demonstrated the antihypertensive effect of dietary protein,<sup>17</sup> a key mechanism that may help preserve diastolic function, the relationship between the amount or source of dietary protein and diastolic function has yet to be assessed. Proteins originating from plants, including legumes, grains, and vegetables, may differentially influence cardiovascular disease risk compared with proteins originating from animals.<sup>18</sup>

We prospectively examined the association of animal and plant food intakes with LVDD, defined via two-dimensional and tissue Doppler echocardiography, among Black and White men and women of the Bogalusa Heart Study (BHS).

## Methods

### Study population

The BHS is an epidemiological study examining the natural history of cardiovascular disease across the lifespan. Between 1973 and 2016, seven surveys of children aged 4–17 as well as 10 surveys of adults, who had been previously observed as children, were completed.<sup>19</sup> There were 524 individuals with dietary and covariable data at baseline (2001 to 2002) who underwent echocardiogram assessment and had an ejection fraction greater than or equal to 55%<sup>20</sup> at follow-up (2013 to 2016), with available measures for all necessary covariables. Among this sample, 10 individuals with a dietary intake of <500 calories or >5000 calories,<sup>21</sup> and 58 individuals on blood pressure (BP), lipid, and/or glucose-lowering therapy were excluded, leaving 456 individuals in the final analysis (Supporting Information, *Figure S1*). The current study sample ( $n = 456$ ) was similar to the full BHS sample ( $n = 1203$ ) at the 2001 to 2002 study visit

(Supporting information, *Table S1*). All of the data were managed using REDcap electronic data capture tools hosted at Tulane University.<sup>22</sup> All study participants provided written informed consent at each examination, and study protocols were approved by the Institutional Review Board of the Tulane University Health Sciences Center.

### Dietary data

Dietary data were collected using the Youth/Adolescent Questionnaire (YAQ), a semiquantitative, validated, 151-item food frequency questionnaire. A food frequency questionnaire approach, as opposed to the 24-h dietary recall method, was used to capture long-term dietary trends.<sup>21</sup> BHS participants were on average 36.1 years old (minimum age: 24.0 years; maximum age: 43.5 years) upon completion of food frequency questionnaires. Previous studies have demonstrated that the YAQ can successfully capture dietary habits and patterns by this young adult population residing in Bogalusa, Louisiana.<sup>23,24</sup> While the average age of participants filling out the YAQ was older than ‘youth’ criteria, investigators chose to use the YAQ at this study survey, between 2001 to 2002, to maintain comparability and reproducibility from previous examinations. We studied several animal and plant food variables and focused on protein as a macronutrient due to previous evidence regarding protein’s role in BP,<sup>17</sup> one upstream determinant of ventricular filling and HF. Food variables included dairy, eggs, red meat, processed meat, poultry, fish, whole grains, legumes, and vegetables. Individual foods included in each respective food variable are presented in Supporting Information, *Table S2*. Nutrient intake analysis, including total protein, dietary animal protein, total alcohol consumption, and total calorie intake, was performed at the Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital at Harvard Medical School, Boston, MA. Foods and nutrients were ranked into tertiles of consumption for statistical analyses.

### Left ventricular diastolic function assessment

Two-dimensional and tissue Doppler echocardiography were performed by trained cardiac sonographers at the BHS field office during the 2013 to 2016 study visit. BHS participants were on average 49.0 years old (minimum age: 36.4 years; maximum age: 56.9 years) at the time of echocardiography. Participants were placed in a partial left lateral decubitus position for echocardiographic assessment. Ten cycles of each two-dimensional and Doppler signal were recorded. Echocardiographic recordings were accomplished using an Aplio 300 ultrasound instrument (Toshiba America Medical Systems, Tustin, CA) with a linear array transducer of 7.5 MHz using

a standard protocol.<sup>25</sup> Left ventricular (LV) ejection fraction was assessed by tracing the endocardial border in the two-chamber view in end systole and end diastole. Diastolic function parameters assessed included early LV filling peak velocity (E), late LV filling peak velocity (A), deceleration time (DT), and isovolumic relaxation time (IVRT). Both the medial and lateral mitral annular velocities ( $e'$ ) were measured using tissue Doppler echocardiography, and we used the average of the two velocities to derive a composite  $E/e'$  ratio.<sup>26</sup> The apical four-chamber view was utilized to assess patterns of mitral inflow including, DT, E wave, A wave, and  $e'$  wave velocities. The E and A wave velocities were assessed using pulsed-wave Doppler echocardiography of transmitral flow at the mitral valve leaflet tips, while medial  $e'$  velocity was measured using pulsed-wave tissue Doppler echocardiography of the mitral annulus. The apical five-chamber view was used to measure IVRT, specifically by placing the sample volume in the LV outflow tract to concurrently evaluate aortic ejection and the onset of mitral inflow. Doppler sample volumes were placed between the mitral leaflet tips to measure DT. Tricuspid regurgitation velocity and left atrial maximum volume index were not measured in early BHS visits; thus, we used the 2016 European Association of Echocardiography/American Society of Echocardiography guidelines to assess diastolic function.<sup>25</sup> Individuals were then grouped as having normal LV diastolic function ( $E/A \geq 0.8$  and  $IVRT < 100$  ms and  $DT < 200$  ms), impaired LV relaxation ( $E/A < 0.8$  and  $IVRT \geq 100$  ms and  $DT \geq 200$  ms), pseudonormal LV filling ( $0.8 < E/A < 1.5$  and medial  $e' < 8$  ms or lateral  $e' < 10$  ms or  $E/e' > 10$ ), and restrictive LV filling ( $E/A \geq 2$  and  $IVRT \leq 60$  ms and  $DT < 160$  ms).<sup>25</sup> LVDD was defined having impaired relaxation, pseudonormal filling, or restrictive filling.<sup>25</sup> Using these guideline-based definitions, there were 13 individuals with impaired LV relaxation and 59 individuals with pseudonormal LV filling, yielding a total of 72 individuals with LVDD in the analysed sample of BHS participants at follow-up.

## Covariates

All covariate data were collected at baseline. Rigorous protocols were employed to collect clinical and sociodemographic data on BHS participants.<sup>27</sup> Validated questionnaires were used to obtain demographic and lifestyle variables, specifically age, race, sex, cigarette smoking, and education status. Cigarette smoking, never vs. former or current, and education status, post-high school educational attainment vs. high school education or below, were both represented as two-level categorical variables. Fasting measures of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, and glucose were collected using standardized methods.<sup>28</sup> BP was measured in triplicate, while height and weight were measured in

duplicate at the time of physical exam. Weight in kilograms was divided by height in metres squared to calculate body mass index (BMI). Serum creatinine was measured using the kinetic Jaffe method. Serum creatinine was used to calculate estimated glomerular filtration rate (eGFR) via the chronic kidney disease epidemiology collaboration equation.<sup>29</sup> Physical activity was assessed through two survey questions 'compared to other people your age and sex, how would you rate your physical activity at work during the past year?' and 'compared to other people your age and sex, how would you rate your physical activity outside of work during the past year?'. Survey responses to these questions were on a 1, inactive, to 5, most active, scale. For the current analysis, the scores for physical activity were added together to generate a continuous 10-point scale, with higher scores reflecting higher levels of physical activity.

## Statistical analysis

Continuous variables were presented as mean  $\pm$  standard deviation, while numbers and percentages were used to present categorical variables. Normality of continuous variables was assessed via the Kolmogorov–Smirnov test. The Student's *t*-test and Wilcoxon signed-rank test were used to assess differences in normally and non-normally distributed continuous variables, respectively. Differences between categorical variables were evaluated using Pearson's chi-square test. We conducted and reported race-stratified and sex-stratified analyses when appropriate. Baseline values for covariates, including age, education, smoking, total calorie intake, alcohol consumption, triglycerides, LDL-C, HDL-C, systolic BP, diastolic BP, BMI, fasting blood glucose, eGFR, and physical activity, were used in multivariable regression models. The associations of dietary protein with risk of LVDD were assessed using three sequentially adjusted multivariable logistic regression models: (i) model 1: sex, race, and age; (ii) model 2: model 1 covariates + education, smoking, total calorie intake, alcohol consumption, natural logarithm of serum triglycerides, LDL-C, and HDL-C; and (iii) model 3: model 2 covariates + systolic BP + diastolic BP + BMI + fasting blood glucose + eGFR. Isocaloric substitution analyses<sup>21</sup> were conducted using the difference in beta coefficients of continuous dietary predictors and were adjusted for model 3 covariates. We conducted three sensitivity analyses: (i) adding physical activity as a covariable to model 3; (ii) excluding individuals ( $n = 141$ ) without baseline echocardiograms from fully adjusted models; and (iii) adjusting for 12-year change in traditional cardiovascular disease risk factors. All hypothesis tests were two-sided and used an alpha threshold of 0.05 for detecting statistically significant differences. Statistical analyses were conducted in SAS Studio (version 3.8; SAS Institute Inc., Cary, NC).

## Results

Table 1 presents the baseline characteristics of the 456 BHS participants (mean age,  $36.1 \pm 4.4$  years; 62.7% women; 26.5% Black) across tertile of total protein consumption. A total of 72 individuals (15.8%) developed LVDD over the study follow-up period (median 12.9 years), and LVDD was significantly associated with tertile of total protein consumption ( $P = 0.03$ ). Sex ( $P < 0.01$ ) and race ( $P = 0.03$ ) significantly associated with protein consumption, as the highest proportions of women (70.4%) and Black individuals (32.2%) were observed among those who consumed less than 50 g of total protein per day. The average daily total energy intake was  $1978.1 \pm 742.6$  kcal, which was within the recommended range (1800 to 2600 kcal per day) for sedentary to moderately active individuals. Contrastingly, participants had a

higher than average daily total protein intake ( $74.3 \pm 29.5$  g per day) compared with the recommended range for middle-aged men and women (46 to 56 g per day). At baseline, individuals on average were overweight (BMI =  $28.7 \pm 6.8$  kg/m<sup>2</sup>) and had normal systolic BP ( $114.5 \pm 11.9$  mmHg) but elevated diastolic BP ( $77.5 \pm 8.8$  mmHg) and elevated LDL-C ( $122.7 \pm 31.7$  mg/dL). Compared with individuals with preserved diastolic function, those with LVDD were significantly older, had higher systolic and diastolic BP, and were more likely to be black (Supporting Information, Table S3).

The associations of animal and plant foods with risk of LVDD are presented in Table 2. Significant quadratic relationships of total protein ( $P$ -trend = 0.003), animal protein ( $P$ -trend = 0.02), processed meat ( $P$ -trend = 0.02), egg ( $P$ -trend = 0.03), fresh vegetable ( $P$ -trend < 0.001), and legume ( $P$ -trend = 0.04) consumption with LVDD were identified,

**Table 1** Characteristics of 456 Bogalusa Heart Study participants by tertile of total protein consumption

Variable	All (n = 456)	Tertile 1 (n = 152)	Tertile 2 (n = 152)	Tertile 3 (n = 152)	P value <sup>a</sup>
Sociodemographic and lifestyle <sup>b</sup>					
Age, years	36.1 (4.4)	36.3 (4.5)	35.7 (4.3)	35.7 (4.3)	0.37
Follow-up time, years	12.9 (12.3, 13.4)	12.8 (12.2, 13.4)	12.9 (12.3, 13.4)	12.9 (12.3, 13.3)	0.65
Female, n (%)	286 (62.7)	107 (70.4)	98 (64.5)	81 (53.3)	0.007
Black, n (%)	121 (26.5)	49 (32.2)	29 (19.1)	43 (28.3)	0.03
Post-high school education, n (%)	205 (44.9)	62 (40.8)	73 (48.0)	70 (46.1)	0.42
Physical activity score	6.0 (5.0, 8.0)	5.8 (4.0, 8.0)	6.1 (5.0, 8.0)	6.3 (5.0, 8.0)	0.26
Alcohol, grams/day	1.8 (2.4)	1.5 (2.3)	1.7 (2.2)	2.1 (2.5)	0.10
Current smoker, n (%)	107 (23.5)	37 (24.3)	30 (19.7)	40 (26.3)	0.38
Dietary intake <sup>b</sup>					
Total energy intake, kcal/day	1978.1 (742.6)	1321.3 (371.9)	1882.7 (332.2)	2730.4 (632.5)	<0.001
Total protein, grams/day	74.3 (29.5)	45.5 (10.1)	70.2 (6.2)	107.2 (23.1)	<0.001
Animal protein, grams/day	51.1 (21.7)	30.6 (8.2)	48.1 (6.9)	74.8 (17.6)	<0.001
Red meat, servings/week	3.0 (1.5, 4.5)	2.0 (1.0, 3.0)	3.0 (2.0, 4.0)	4.5 (3.5, 6.0)	<0.001
Processed meat, servings/week	3.5 (2.5, 5.0)	2.5 (1.5, 3.5)	3.5 (2.8, 4.5)	5.0 (3.5, 7.0)	<0.001
Chicken, servings/week	1.0 (0.5, 3.0)	0.5 (1.5, 3.5)	1.0 (0.5, 3.0)	3.0 (1.0, 3.0)	<0.001
Fish, servings/week	1.0 (0.5, 1.5)	0.5 (0.5, 1.0)	1.0 (0.5, 1.0)	1.5 (1.0, 2.0)	<0.001
Dairy intake, servings/week	5.0 (2.0, 8.0)	2.3 (1.0, 5.0)	5.0 (2.0, 8.0)	8.0 (5.0, 11.3)	<0.001
Egg intake, servings/week	1.0 (0.5, 3.0)	0.5 (0.5, 3.0)	1.0 (0.5, 3.0)	3.0 (1.0, 3.0)	<0.001
Fresh vegetables, servings/week	7.0 (4.0, 11.5)	5.0 (3.0, 8.0)	6.5 (4.5, 10.5)	10.5 (6.3, 16.0)	<0.001
Legumes, servings/week	1.5 (1.0, 3.5)	1.3 (0.5, 1.5)	1.5 (1.0, 4.0)	2.0 (1.5, 4.5)	<0.001
Whole grains, servings/week	1.0 (0.5, 3.5)	0.5 (0.0, 3.0)	1.5 (0.5, 3.3)	2.0 (0.5, 6.0)	<0.001
Cardiovascular disease risk factors <sup>b</sup>					
Systolic blood pressure, mmHg	114.5 (11.9)	114.6 (12.7)	113.8 (12.0)	115.1 (11.2)	0.64
Diastolic blood pressure, mmHg	77.5 (8.8)	78.0 (9.3)	76.8 (8.6)	77.8 (8.3)	0.43
BMI, kg/m <sup>2</sup>	28.7 (6.8)	28.6 (7.1)	28.5 (6.5)	28.9 (6.8)	0.89
LDL cholesterol, mg/dL	122.7 (31.7)	123.3 (31.0)	124.2 (32.5)	120.5 (31.7)	0.56
HDL cholesterol, mg/dL	48.3 (13.4)	48.5 (12.0)	48.8 (13.9)	47.6 (14.1)	0.71
Fasting blood glucose, mg/dL	83.6 (14.8)	81.9 (9.0)	84.0 (20.8)	84.9 (12.0)	0.19
Serum triglycerides, mg/dL	99.0 (72.0, 144.0)	119.5 (71.5, 143.5)	127.7 (78.5, 143.0)	126.0 (70.5, 147.0)	0.69
eGFR, mL/min/1.73m <sup>2</sup>	104.6 (16.6)	104.5 (16.6)	104.7 (16.3)	104.5 (17.1)	0.99
Imaging <sup>c</sup>					
Ejection fraction, %	64.0 (3.9)	64.0 (3.6)	64.2 (4.6)	63.8 (3.5)	0.60
E/A ratio	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	0.92
E/e' ratio	6.7 (1.8)	6.7 (1.7)	6.8 (1.9)	6.7 (1.8)	0.82
Deceleration time, ms	187.9 (46.4)	187.1 (44.3)	189.0 (47.6)	187.7 (47.6)	0.93
Isovolumic relaxation time, ms	93.5 (21.9)	90.6 (21.4)	94.9 (22.1)	95.0 (22.0)	0.13
Left ventricular diastolic dysfunction, n (%)	72 (15.8)	17 (11.2)	33 (21.7)	22 (14.7)	0.03

Mean and standard deviation presented for normally distributed continuous variables; median and quartile 1 and quartile 3 presented for non-normally distributed continuous variables.

<sup>a</sup>ANOVA test for continuous variables and chi-square test for categorical variables.

<sup>b</sup>Collected at baseline.

<sup>c</sup>Collected at follow-up.

**Table 2** Consumption of animal and plant foods and risk of left ventricular diastolic dysfunction

Dietary predictor	Tertile 1 (n = 152)	Tertile 2 (n = 152)	Tertile 3 (n = 152)	Overall P value	Linear trend	Quadratic trend
	OR (95% CI)	OR (95% CI)	OR (95% CI)			
<b>Total protein, grams/day</b>						
Model 1	Ref	2.73 (1.40, 5.31)	1.54 (0.76, 3.11)	0.01	0.36	0.003
Model 2	Ref	3.19 (1.48, 6.90)	2.07 (0.68, 6.33)	0.007	0.28	0.003
Model 3	Ref	3.30 (1.46, 7.45)	2.12 (0.67, 6.71)	0.009	0.32	0.003
<b>Animal protein, grams/day</b>						
Model 1	Ref	2.52 (1.29, 4.92)	1.74 (0.87, 3.47)	0.03	0.17	0.01
Model 2	Ref	2.84 (1.36, 5.94)	2.38 (0.88, 6.41)	0.02	0.11	0.02
Model 3	Ref	2.91 (1.34, 6.34)	2.51 (0.90, 7.02)	0.03	0.11	0.02
<b>Red meat, servings/week</b>						
Model 1	Ref	0.98 (0.52, 1.86)	1.18 (0.63, 2.21)	0.82	0.57	0.77
Model 2	Ref	0.98 (0.50, 1.91)	1.14 (0.56, 2.31)	0.90	0.70	0.82
Model 3	Ref	0.79 (0.39, 1.60)	1.13 (0.54, 2.36)	0.59	0.64	0.36
<b>Processed meat, servings/week</b>						
Model 1	Ref	2.60 (1.30, 5.23)	1.95 (0.94, 4.04)	0.03	0.20	0.01
Model 2	Ref	2.70 (1.28, 5.70)	2.05 (0.89, 4.75)	0.03	0.29	0.01
Model 3	Ref	2.64 (1.22, 5.72)	2.00 (0.84, 4.78)	0.05	0.33	0.02
<b>Chicken, servings/week</b>						
Model 1	Ref	0.88 (0.47, 1.66)	0.70 (0.37, 1.31)	0.52	0.26	0.86
Model 2	Ref	0.88 (0.46, 1.70)	0.73 (0.37, 1.44)	0.66	0.38	0.84
Model 3	Ref	0.82 (0.41, 1.65)	0.72 (0.36, 1.45)	0.65	0.40	0.69
<b>Fish, servings/week</b>						
Model 1	Ref	1.70 (0.92, 3.15)	1.17 (0.59, 2.31)	0.22	0.82	0.08
Model 2	Ref	1.73 (0.92, 3.24)	1.18 (0.57, 2.45)	0.21	0.81	0.08
Model 3	Ref	1.54 (0.80, 2.96)	1.10 (0.51, 2.37)	0.39	0.95	0.17
<b>Dairy, servings/week</b>						
Model 1	Ref	1.02 (0.53, 1.95)	1.05 (0.56, 1.97)	0.99	0.87	0.98
Model 2	Ref	0.93 (0.48, 1.84)	0.92 (0.46, 1.84)	0.97	0.81	0.92
Model 3	Ref	1.08 (0.53, 2.19)	0.88 (0.42, 1.83)	0.86	0.74	0.65
<b>Eggs, servings/week</b>						
Model 1	Ref	2.11 (0.97, 4.57)	1.28 (0.71, 2.32)	0.17	0.77	0.06
Model 2	Ref	2.28 (1.02, 5.08)	1.26 (0.66, 2.40)	0.12	0.94	0.04
Model 3	Ref	2.47 (1.07, 5.69)	1.32 (0.66, 2.63)	0.09	0.92	0.03
<b>Fresh vegetables, servings/week</b>						
Model 1	Ref	0.28 (0.14, 0.57)	0.59 (0.32, 1.08)	0.002	0.27	0.001
Model 2	Ref	0.27 (0.13, 0.55)	0.56 (0.29, 1.10)	0.002	0.27	<0.001
Model 3	Ref	0.23 (0.11, 0.49)	0.47 (0.23, 0.96)	<0.001	0.14	<0.001
<b>Legumes, servings/week</b>						
Model 1	Ref	0.47 (0.25, 0.88)	0.54 (0.28, 1.03)	0.04	0.13	0.04
Model 2	Ref	0.46 (0.25, 0.88)	0.51 (0.25, 1.03)	0.04	0.13	0.04
Model 3	Ref	0.44 (0.22, 0.85)	0.44 (0.21, 0.94)	0.02	0.08	0.04
<b>Whole grains, servings/week</b>						
Model 1	Ref	0.85 (0.43, 1.70)	0.81 (0.45, 1.47)	0.78	0.53	0.75
Model 2	Ref	0.88 (0.43, 1.78)	0.84 (0.45, 1.55)	0.85	0.61	0.79
Model 3	Ref	0.90 (0.43, 1.90)	0.91 (0.47, 1.74)	0.95	0.81	0.82

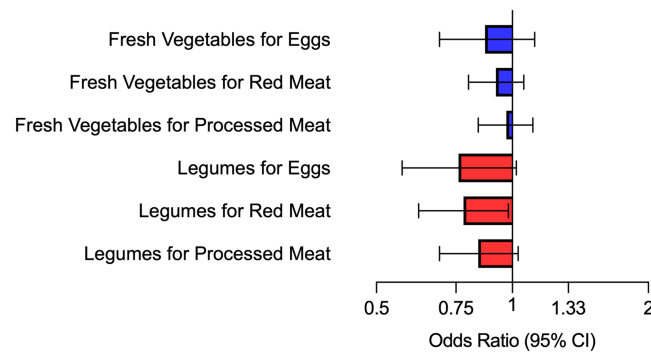
Model 1: adjusted for age, sex, and race. Model 2: adjusted for age, sex, race, education, smoking, total energy intake, alcohol consumption, serum triglycerides, LDL-C, and HDL-C. Model 3: adjusted for age, sex, race, education, smoking, total energy intake, alcohol consumption, serum triglycerides, LDL-C, HDL-C, systolic blood pressure, diastolic blood pressure, BMI, and fasting blood glucose, eGFR

such that individuals in the middle tertile were observed to have either the highest or lowest risk of LVDD depending on the respective dietary variable. Compared with individuals in the lowest tertile, persons in the middle tertile of total protein intake were 3.3 times more likely to develop LVDD, which was the highest magnitude parameter estimate observed among all dietary correlates. Individuals in the middle tertile of animal protein, processed meat, and egg intake all had a twofold to threefold significantly higher risk of LVDD when compared with individuals in the lowest tertile of each respective dietary correlate.

Higher fresh vegetable and legume intake showed protective associations with LVDD, with significant quadratic trends

again observed. Individuals in the middle and highest tertile of fresh vegetables consumption per week had at least a 53% lower risk of developing LVDD compared with persons with the lowest tertile of consumption. Similarly, persons in the middle and highest tertile of legume intake were 56% less likely to develop LVDD when compared with those in the lowest tertile of legume intake. Among significant dietary predictors, there was an overall pattern towards decreased risk of LVDD upon replacing plant foods for animal foods in isocaloric substitution analyses (*Figure 1*). After controlling for traditional cardiovascular disease risk factors, replacing one weekly serving of legumes for red meat conferred a 22% risk reduction for LVDD (OR = 0.78, 95% CI: 0.62, 0.98).



**Figure 1** Estimated reduction in risk of left ventricular diastolic dysfunction associated with isocaloric substitution of plant foods for animal foods.

No significant associations or trends of LVDD with red meat, chicken, fish, dairy, or whole grains were observed. Results from the sensitivity analyses, additionally adjusting model 3 for physical activity, excluding participants without baseline echocardiography, and adjusting for 12-year change in traditional CVD risk factors are presented in Supporting Information, *Tables S4–S6*. Overall, odds ratios and *P* values in the sensitivity analyses were consistent with primary study results presented in *Table 2*.

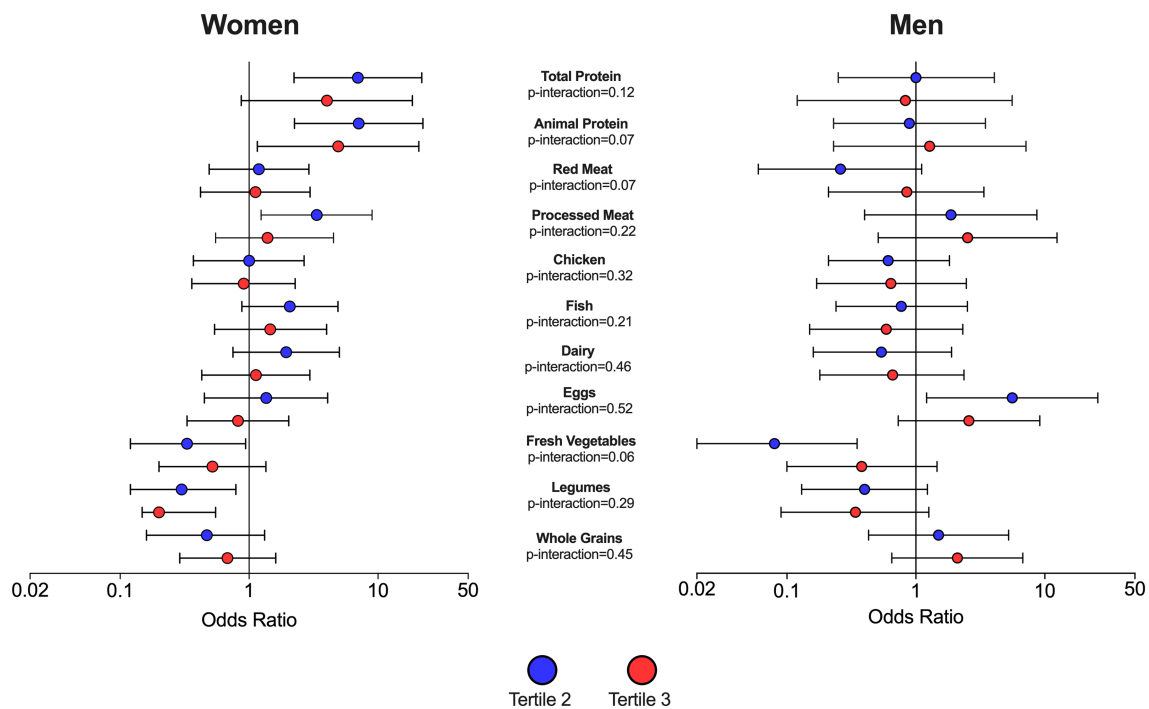
*Figure 2* displays the associations of each dietary predictor with LVDD, stratified by sex. Although sex did not significantly modify the association of any dietary factor with LVDD, marginally significant interactions of sex with total protein, animal protein, red meat, and fresh vegetables on LVDD were observed (all *P*-interaction  $< 0.0003$ ;  $0.15$ ). Total protein and animal protein conferred higher risks of LVDD in women but not men (*P*-interaction =  $0.12$  and  $0.07$ , respectively). In addition, fresh vegetable consumption tended to have larger protective effects in men compared with women (*P*-interaction =  $0.06$ ). Race did not significantly modify the association of plant or animal foods with LV diastolic function.

## Discussion

Our results suggest that dietary intake patterns in young adulthood serve as important modifiable risk factors for the development of LVDD in midlife among Black and White men and women. In particular, higher consumption of plant food sources, including vegetables and legumes, may help protect against future development of LVDD, while regular intake of animal protein and processed meat may increase risk of LVDD and broader long-term cardiometabolic disease. These findings suggest that dietary improvements at the population level may help prevent LVDD and subsequent development of HFpEF over time.

Our study is the first to analyse the association between dietary protein and LV diastolic function, and these results fit into a broader context of research regarding protein consumption and cardiometabolic disease. For example, analyses in over 2000 Finnish men in the Kuopio Ischemic Heart Disease Risk Factor Study identified a significant linear trend in increased risk for incident HF with higher dietary intake of total protein, as well as dairy protein.<sup>30</sup> Similar findings have also been observed in more diverse cohorts, suggesting that adherence to plant-based dietary patterns inversely associates with HF risk<sup>15</sup> and that replacing animal protein or processed meat with plant protein associates with lower total and cardiovascular disease mortality.<sup>31,32</sup> We found that a higher intake of total protein, animal protein, processed meat, and eggs showed a significant quadratic trend towards increased risk of LVDD, while vegetables and legumes exhibited a quadratic trend towards decreased LVDD risk among Black and White men and women. The threshold effects observed here suggest that dietary patterns may appreciably influence LVDD risk up to a certain extent, past which more traditional upstream determinants, including BP,<sup>33</sup> BMI,<sup>33</sup> insulin sensitivity,<sup>34</sup> and kidney function<sup>35</sup> may more largely impact the development of LVDD and HFpEF. Diets high in protein and red meat have previously been associated with an increased incidence of chronic kidney disease<sup>36</sup> as well as type 2 diabetes,<sup>37</sup> two independent risk factors for HF. In addition, dietary threshold effects have also been previously reported for other subclinical cardiovascular disease phenotypes including the relationship between dietary cholesterol and dyslipidemia.<sup>38</sup>

We observed a 22% lower risk of LVDD upon replacement of one weekly serving of red meat for legumes over a 12-year period. Animal-derived and plant-derived proteins have different amino acid compositions, and these biochemical differences may be important drivers or modifiers in their relationship with cardiometabolic health. Branched-chain amino acids, leucine, isoleucine, and valine are higher in

**Figure 2** Consumption of animal and plant foods and risk of left ventricular diastolic dysfunction, stratified by sex.

animal protein-based diets compared with plant-based diets<sup>39,40</sup> and appear to confer an increased risk of type 2 diabetes<sup>41</sup> and cardiovascular disease,<sup>42</sup> particularly in women.<sup>43</sup> Branched-chain amino acid catabolism is also impaired in the failing heart.<sup>44</sup> We found a higher risk of LVDD conferred by increased dietary intakes of both animal protein and processed meat, with sex-stratified analyses demonstrating a trend towards higher risk of LVDD with increased intake of total protein and animal protein in women but not men. These results suggest that biological sex may potentially modify the association of animal protein with LV diastolic function, such that dietary protein and branched-chain amino acid metabolism may have unique pathophysiological roles in women vs. men. For example, the positive association between branched-chain amino acids and CVD has noted to be more prominent in women vs. men.<sup>43</sup> Likewise, there may be gonadal hormone regulation of both upstream (e.g. microbiome-dependent metabolism) and downstream (e.g. amino acid catabolism) pathways that contribute to observed sex differences<sup>45</sup> in the role of dietary protein in CVD and LV diastolic function. Given our relatively small sample size and the complexity of dietary protein metabolism, subgroup analyses in men and women in the current study should be cautiously interpreted. Furthermore, while Blacks demonstrate a higher prevalence of undiagnosed hypertension compared with Whites,<sup>46</sup> our study did not observe any race-specific effect of diet on LVDD.

The relationships of dietary protein sources with LV diastolic function we identified in this study are both novel and salient. There are several mechanisms that may contribute to a lower risk of LVDD and HFpEF with higher intake of vegetables and legumes, including physiological effects related to isoflavones, fibre, potassium and magnesium. Dietary isoflavones, obtained through soy-based foods such as tofu and tempeh, independently associate with lower systolic BP and may exert their effects through endothelium-dependent vasodilation.<sup>47</sup> Soy protein is rich in arginine, an essential component of the nitric oxide pathway, which may help promote vasodilation.<sup>48</sup> Moreover, vegetables are rich in potassium, a micronutrient that has also been shown to reduce BP in randomized controlled trials.<sup>49</sup> Vegetables and legumes are also excellent sources of dietary fibre, a macronutrient that can improve insulin sensitivity,<sup>50</sup> reduce total and LDL-C,<sup>50</sup> and lower BP.<sup>51</sup> Individuals who obtain most of their calories and protein from animal sources may not derive these latter dietary benefits from vegetables and legumes and may also have higher exposure to sodium that often accompanies animal protein and processed meat intake.<sup>52</sup> Dietary exposure to high sodium and oxidized proteins through processed meats and animal protein consumption may be a key contributor to the heightened cardiometabolic risk that is consistently observed upon regular consumption of these foods.<sup>53,54</sup> Furthermore, while low-carbohydrate/high-protein diets have been previously shown

to reduce cardiovascular disease risk,<sup>55</sup> we identified a deleterious association between higher total protein intake and LVDD. This result was driven by animal protein and processed meat, suggesting that the dietary source (plant vs. animal) of macronutrients may be just as important as the quantity of macronutrient intake. Additional research is required to disentangle the most optimal balance of dietary animal and plant protein for LVDD, HFpEF, and broader cardiometabolic disease prevention.

Our study had several strengths, including a high proportion of both women (62%) and Black participants (25%). Although female gender is a robust differentiating characteristic of HFpEF compared with HF with reduced ejection fraction,<sup>56,57</sup> women are still underrepresented in HF<sup>58</sup> and broader cardiometabolic clinical trials.<sup>59</sup> These observed gender disparities suggest the presence of sex-specific mechanisms of ventricular pathobiology and a need to include more women in aetiologic studies of HFpEF. Here, we show that plant-based protein may be of importance for the preservation of diastolic function among a sample comprised of nearly two-thirds women; thus, our findings are both clinically relevant and generalizable for targeted HFpEF prevention efforts.

On the other hand, our findings should also be interpreted in the setting of limitations. Only 315 out of 456 participants in the current study had baseline echocardiography data and tissue Doppler parameter,  $e'$ , was not measured during this BHS Visit. However, none of the 315 individuals exhibited impaired LV relaxation as measured by E/A ratio, IVRT, and DT, which is the initial insult on the LVDD biological cascade, and results excluding those without baseline echocardiography were consistent compared with main study findings. Given these data and the young age of participants at baseline, the presence of LVDD at baseline was exceedingly unlikely.<sup>60</sup> Additionally, dietary data for this study were collected only at baseline, preventing the analysis of change in dietary habits over time. Likewise, we were unable to assess the role of inflammatory markers as they relate to diet, oxidative stress, and cardiac remodelling in the setting of LVDD. Studies of diet and LVDD should strive to incorporate novel markers, such as high-sensitivity C-reactive protein (inflammation), osteopontin (remodelling), and neuropilin (angiogenesis).<sup>61</sup> Finally, although logistic regression models were adjusted for several traditional cardiometabolic factors and lifestyle variables, residual confounding may have affected our results and is a limitation shared among all observational study designs.

In conclusion, we have observed that a higher intake of total protein, animal protein, processed meat, and eggs conferred higher risks of LVDD, while higher legume and fresh vegetable intake conferred lower risks of LVDD. Observed quadratic trends suggest the presence of a threshold effect, such that diet may influence risk of LVDD and future HFpEF

up to a certain extent, past which traditional cardiometabolic determinants occupy or mediate a larger role in ventricular function. Our findings support the notion that adherence to consuming predominantly plant-based protein may help preserve LV function over time and reduce the burden of HFpEF in the general population.

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## Conflict of interest

None declared.

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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Comparison of Bogalusa Heart Study Samples

**Table S2.** Individual Components of Food Source Variables

**Table S3.** Characteristics of 456 Bogalusa study participants, stratified by LVDD status

**Table S4.** Consumption of Animal and Plant Foods and Risk of Left Ventricular Diastolic Dysfunction, Additionally Adjusting for Physical Activity (n = 456)

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**Table S5.** Consumption of Animal and Plant Foods and Risk of



Left Ventricular Diastolic Dysfunction Among Those with Baseline Echocardiography (n = 315)

**Table S6.** Consumption of Animal and Plant Foods and Risk of

Left Ventricular Diastolic Dysfunction, Adjusting for Change in Traditional Cardiovascular Disease Risk Factors from Baseline

to Follow-Up (n = 434)

## References

- Vigen R, Maddox TM, Allen LA. Aging of the United States population: impact on heart failure. *Curr Heart Fail Rep* 2012; **9**: 369–374.
- Ziaieian B, Fonarow GC. Epidemiology and aetiology of heart failure. *Nat Rev Cardiol* 2016; **13**: 368–378. Available from: <http://www.nature.com/articles/nrcardio.2016.25>
- Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. *Circulation* 2017; **135**: e146–e603.
- Dunlay SM, Roger VL, Redfield MM. *Epidemiology of heart failure with preserved ejection fraction*, Vol. **14**. *Nat Rev Cardiol*; 2017. p 591–602.
- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, RosanoGMC RLM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129–2200.
- Borlaug BA, Redfield MM, Melenovsky V, Kane GC, Karon BL, Jacobsen SJ, Rodeheffer RJ. Longitudinal changes in left ventricular stiffness. *Circ Heart Fail* 2013; **6**: 944–952.
- Kane GC, Karon BL, Mahoney DW, Redfield MM, Roger VL, Burnett JC, Jacobsen SJ, Rodeheffer RJ. Progression of left ventricular diastolic dysfunction and risk of heart failure. *JAMA* 2011; **306**: 856–863.
- Halley CM, Houghtaling PL, Khalil MK, Thomas JD, Jaber WA. Mortality rate in patients with diastolic dysfunction and normal systolic function. *Arch Intern Med* 2011; **171**: 1082–1087.
- Gorcsan J III, Diana P, Lee J, Katz WE, Hattler BG. Reversible diastolic dysfunction after successful coronary artery bypass surgery: assessment by transesophageal Doppler echocardiography. *Chest* 1994; **106**: 1364–1369.
- Lee CH, Hung KC, Chang SH, Lin FC, Hsieh MJ, Chen CC, Chu CM, Hsieh IC, Wen MS, Wu D. Reversible left ventricular diastolic dysfunction on Doppler tissue imaging predicts a more favorable prognosis in chronic heart failure. *Circ J [Internet]* 2012 [cited 2019 Mar 18]; **76**: 1145–1150. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22354196>
- Meyer TE, Kovács SJ, Ehsani AA, Klein S, Holloszy JO, Fontana L. Long-term caloric restriction ameliorates the decline in diastolic function in humans. *J Am Coll Cardiol* 2006; **47**: 398–402.
- von Bibra H, Ströhle A, St. John Sutton M, Worm N. Dietary therapy in heart failure with preserved ejection fraction and/or left ventricular diastolic dysfunction in patients with metabolic syndrome. *Int J Cardiol* 2017; **234**: 7–15.
- Tektonidis TG, Åkesson A, Gigante B, Wolk A, Larsson SC. A Mediterranean diet and risk of myocardial infarction, heart failure and stroke: a population-based cohort study. *Atherosclerosis* 2015; **243**: 93–98.
- Leviton EB, Wolk A, Mittleman MA. Consistency with the DASH diet and incidence of heart failure. *Arch Intern Med* 2009; **169**: 851–857.
- Lara KM, Levitan EB, Gutierrez OM, Shikany JM, Safford MM, Judd SE, Rosenson RS. Dietary patterns and incident heart failure in US adults without known coronary disease. *J Am Coll Cardiol* 2019; **73**: 2036–2045.
- Maugeri A, Hruskova J, Jakubik J, Hlinomaz O, Medina-Inojosa JR, Barchitta M, Agodi A, Vinciguerra M. How dietary patterns affect left ventricular structure, function and remodeling: evidence from the Kardioviez Brno 2030 study. *Sci Rep* 2019; **9**: 1–10.
- Rebholz CM, Friedman EE, Powers LJ, Arroyave WD, He J, Kelly TN. Dietary protein intake and blood pressure: a meta-analysis of randomized controlled trials. *Am J Epidemiol* 2012; **176**: S27–S43.
- Richter CK, Skulas-Ray AC, Champagne CM, Kris-Etherton PM. Plant protein and animal proteins: do they differentially affect cardiovascular disease risk? *Adv Nutri* 2015; **6**: 712–728.
- Berenson GS, Bogalusa Heart Study Investigators. Bogalusa Heart Study: a long-term community study of a rural biracial (Black/White) population. *Am J Med Sci* 2001; **322**: 293–300.
- Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; **18**: 1440–1463.
- Willett W. Nutritional epidemiology. *Teaching Epidemiology: A Guide for Teachers in Epidemiology*. Public Health and Clinical Medicine; 2016 March 26:157.
- Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42**: 377–381.
- Rockett HR, Breitenbach M, Frazier AL, Witschi J, Wolf AM, Field AE, Colditz GA. Validation of a youth/adolescent food frequency questionnaire. *Prev Med* 1997; **26**: 808–816.
- Deshmukh-Taskar PR, O'Neil CE, Nicklas TA, Yang SJ, Liu Y, Gustat J, Berenson GS. Dietary patterns associated with metabolic syndrome, sociodemographic and lifestyle factors in young adults: the Bogalusa Heart Study. *Public Health Nutr* 2009; **12**: 2493–2503.
- Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P.

- Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2016; **17**: 1321–1360.
26. Sharp AS, Tapp RJ, Thom SA, Francis DP, Hughes AD, Stanton AV, Zambanini A, O'Brien E, Chaturvedi N, Lyons S, Byrd S. Tissue Doppler E/E' ratio is a powerful predictor of primary cardiac events in a hypertensive population: an ASCOT substudy. *Eur Heart J* 2010; **31**: 747–752.
  27. Foster TA, Berenson GS. Measurement error and reliability in four pediatric cross-sectional surveys of cardiovascular disease risk factor variables—the Bogalusa Heart Study. *J Chronic Dis* 1987; **40**: 13–21.
  28. Bogalusa Heart Study protocol [Internet]. 1995 [cited 2019 Apr 3]. Available from: [https://biolincc.nhlbi.nih.gov/media/studies/bhs/Adult\\_Exam\\_Protocol.pdf?link\\_time=2019-04-03\\_12:53:51.100096](https://biolincc.nhlbi.nih.gov/media/studies/bhs/Adult_Exam_Protocol.pdf?link_time=2019-04-03_12:53:51.100096)
  29. Levey AS, Stevens LA. Estimating GFR Using the CKD epidemiology collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. *Am J Kidney Dis* 2010; **55**: 622–627.
  30. Virtanen HEK, Voutilainen S, Koskinen TT, Mursu J, Tuomainen T-P, Virtanen JK. Intake of different dietary proteins and risk of heart failure in men. *Circ Heart Fail* 2018; **11**: e004531.
  31. Virtanen HE, Voutilainen S, Koskinen TT, Mursu J, Kokko P, Ylilauri M, Tuomainen TP, Salonen JT, Virtanen JK. Dietary proteins and protein sources and risk of death: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Am J Clin Nutr* 2019; **109**: 1462–1471.
  32. Budhathoki S, Sawada N, Iwasaki M, Yamaji T, Goto A, Kotemori A, Ishihara J, Takachi R, Charvat H, Mizoue T, Iso H. Association of animal and plant protein intake with all-cause and cause-specific mortality in a Japanese cohort. *JAMA Intern Med* 2019; **179**: 1509–1518.
  33. Heiskanen JS, Ruohonen S, Rovio SP, Kytö V, Kähönen M, Lehtimäki T, Viikari JS, Juonala M, Laitinen T, Tossavainen P, Jokinen E. Determinants of left ventricular diastolic function—the Cardiovascular Risk in Young Finns Study. *Echocardiography* 2019; **36**: 854–861.
  34. Poulsen MK, Henriksen JE, Dahl J, Johansen A, Gerke O, Vach W, Haghfelt T, Hilund-Carlson PF, Beck-Nielsen H. Left ventricular diastolic function in type 2 diabetes mellitus: prevalence and association with myocardial and vascular disease. *Circ Cardiovasc Imaging* 2010; **3**: 24–31.
  35. Ogawa T, Nitta K. Clinical impact of left ventricular diastolic dysfunction in chronic kidney disease. *Contrib Nephrol* 2018; 81–91.
  36. Mirmiran P, Yuzbashian E, Aghayan M, Mahdavi M, Asghari G, Azizi F. A prospective study of dietary meat intake and risk of incident chronic kidney disease. *J Ren Nutr* 2019; **30**: 111–118.
  37. Adeva-Andany MM, González-Lucán M, Fernández-Fernández C, Carneiro-Freire N, Seco-Filgueira M, Pedre-Piñeiro AM. Effect of diet composition on insulin sensitivity in humans. *Clin Nutr ESPEN* 2019; **33**: 29–38.
  38. Huang Q, Jiang H, Zhang B, Wang H, Jia X, Huang F, Wang L, Wang Z. Threshold-effect association of dietary cholesterol intake with dyslipidemia in Chinese adults: results from the China Health and Nutrition Survey in 2015. *Nutrients* 2019; **11**: 2885.
  39. Wyness L. The role of red meat in the diet: nutrition and health benefits. *Proc Nutr Soc* 2016; **75**: 227–2732.
  40. Millward DJ, Layman DK, Tomé D, Schaafsma G. Protein quality assessment: impact of expanding understanding of protein and amino acid needs for optimal health. *Am J Clin Nutr* 2008; **87**: 1576S–1581S.
  41. Adeva MM, Calviño J, Souto G, Donapetry C. Insulin resistance and the metabolism of branched-chain amino acids in humans. *Amino Acids*; **43**: 171–181.
  42. Ruiz-Canela M, Toledo E, Clish CB, Hruby A, Liang L, Salas-Salvadó J, Razquin C, Corella D, Estruch R, Ros E, Fitó M. Plasma branched-chain amino acids and incident cardiovascular disease in the PREDIMED trial. *Clin Chem* 2016; **62**: 582–592.
  43. Tobias DK, Lawler PR, Harada PH, Demler OV, Ridker PM, Manson JE, Cheng S, Mora S. Circulating branched-chain amino acids and incident cardiovascular disease in a prospective cohort of US women. *Circu: Genomic Precision Med* 2018; **11**: e002157.
  44. Sun H, Olson KC, Gao C, Prosdocimo DA, Zhou M, Wang Z, Jeyaraj D, Youn JY, Ren S, Liu Y, Rau CD. Catabolic defect of branched-chain amino acids promotes heart failure. *Circulation* 2016; **133**: 2038–2049.
  45. Razavi AC, Potts KS, Kelly TN, Bazzano LA. Sex, gut microbiome, and cardiovascular disease risk. *Biol Sex Differ* 2019; **10**: 29.
  46. Carnethon MR, Pu J, Howard G, Albert MA, Anderson CA, Bertoni AG, Mujahid MS, Palaniappan L, Taylor HA Jr, Willis M, Yancy CW. Cardiovascular health in African Americans: a scientific statement from the American Heart Association. *Circulation* 2017; **136**: e393–e423.
  47. Richardson SI, Steffen LM, Swett K, Smith C, Burke L, Zhou X, Shikany JM, Rodriguez CJ. Dietary total isoflavone intake is associated with lower systolic blood pressure: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *J Clin Hypertens (Greenwich)* 2016; **18**: 778–783.
  48. Wong WW, Taylor AA, Smith EO, Barnes S, Hachey DL. Effect of soy isoflavone supplementation on nitric oxide metabolism and blood pressure in menopausal women. *Am J Clin Nutr* 2012; **95**: 1487–1494.
  49. Sacks FM, Willett WC, Smith A, Brown LE, Rosner B, Moore TJ. Effect on blood pressure of potassium, calcium, and magnesium in women with low habitual intake. *Hypertens* 1998; **31**: 131–138.
  50. Weickert MO, Pfeiffer AF. Impact of dietary fiber consumption on insulin resistance and the prevention of type 2 diabetes. *J Nutr* 2018; **148**: 7–12.
  51. Streppel MT, Arends LR, van't Veer P, Grobbee DE, Geleijnse JM. Dietary fiber and blood pressure. *Arch Intern Med* 2005; **165**: 150–156.
  52. Montenegro-Bethancourt G, Johnner SA, Stehle P, Remer T. Dietary ratio of animal: plant protein is associated with 24-h urinary iodine excretion in healthy school children. *Br J Nutr* 2015; **114**: 24–33.
  53. Estévez M, Xiong Y. Intake of oxidized proteins and amino acids and causative oxidative stress and disease: recent scientific evidences and hypotheses. *J Food Sci* 2019; **84**: 387–396.
  54. He J, Ogden LG, Vupputuri S, Bazzano LA, Loria C, Whelton PK. Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults. *JAMA* 1999; **282**: 2027–2034.
  55. Bazzano LA, Hu T, Reynolds K, Yao L, Bunol C, Liu Y, Chen CS, Klag MJ, Whelton PK, He J. Effects of low-carbohydrate and low-fat diets: a randomized trial. *Ann Intern Med* 2014; **161**: 309–318.
  56. Ho JE, Gona P, Pencina MJ, Tu JV, Austin PC, Vasan RS, Kannel WB, D'Agostino RB, Lee DS, Levy D. Discriminating clinical features of heart failure with preserved vs. reduced ejection fraction in the community. *Eur Heart J*; **33**: 1734–1741.
  57. Beale AL, Meyer PMD, Marwick TH, Lam CSP, Kaye DM. Sex differences in cardiovascular pathophysiology why women are overrepresented in heart failure with preserved ejection fraction. *Circulation* 2018; **138**: 198–205.
  58. Tahhan AS, Vaduganathan M, Greene SJ, Fonarow GC, Fiuzat M, Jessup M, Lindenfeld J, O'Connor CM, Butler J. Enrollment of older patients, women, and racial and ethnic minorities in contemporary heart failure clinical trials: a systematic review. *JAMA Cardiol* 2018; **3**: 1011–1019.
  59. Khan MS, Shahid I, Siddiqi TJ, Khan SU, Warraich HJ, Greene SJ, Butler J, Michos ED. Ten-year trends in enrollment of women and minorities in pivotal trials supporting recent US Food and Drug Administration approval of novel cardiometabolic drugs. *J Am Heart Assoc* 2020; **9**: e015594.

60. Schmitz L, Koch H, Bein G, Brockmeier K. Left ventricular diastolic function in infants, children, and adolescents. Reference values and analysis of morphologic and physiologic determinants of echocardiographic Doppler flow signals during growth and maturation. *J Am Coll Cardiol* 1998; **32**: 1441–1448.
61. Tromp J, Khan MA, Klip IT, Meyer S, de Boer RA, Jaarsma T, Hillege H, van Veldhuisen DJ, van der Meer P, Voors AA. Biomarker profiles in heart failure patients with preserved and reduced ejection fraction. *J Am Heart Assoc* 2017; **6**: e003989.