British Journal of Nutrition (2023), 130, 467–475 doi:10.1017/S0007114522003348

Left ventricular diastolic abnormalities in vegetarians compared with non-vegetarians

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(Submitted 19 May 2022 – Final revision received 25 August 2022 – Accepted 7 October 2022 – First published online 20 October 2022)

Abstract

Vegetarians have less hypertension, diabetes mellitus and obesity, hence possibly lower risk of congestive heart failure (HF). We studied associations between vegetarian diets and echocardiographic markers of stage B HF. In a cross-sectional study, dietary pattern was ascertained by a validated FFQ. Echocardiograms were interpreted using standardised criteria. Participants were free-living subjects in Southern California who were older Adventist Health Study-2 cohort members. After exclusions, 133 subjects aged >60 years were enrolled. Their mean age was 72·7 (SD 8·7) years, 48·1 % were female, 32 % were African American and 71 % were vegetarian. Non-vegetarians had higher body weight (80·3 (SD 15·17) kg *v.* 71·3 (SD 16·2), $P < 0·005$), body surface area (1·92 (SD 0·24) m^2 *v.* 1·81 (SD 0·22) m^2, $P = 0·01$) and prevalence of hypertension (63 % *v.* 47 %, $P = 0·10$). Adjusting for age, sex, race and physical activity, it is found that vegetarians had greater echocardiographic mitral annular e' velocity (a measure of left ventricular (LV) relaxation) 7·44 *v.* 6·48 (non-vegetarian) cm/s ($P = 0·011$) and a yet greater contrast when vegans (7·66 cm/s, $P = 0·011$) were the group of interest. The ratio mid-to-late-diastolic mitral flow velocity (E/A) was also higher in vegans compared with non-vegetarians (1·02 and 0·84, respectively, $P = 0·008$). Mediation analyses suggested these associations may be partly related to higher blood pressures and BMI in the non-vegetarians. We conclude that vegetarians, especially vegans, appear to have better LV relaxation and fewer diastolic abnormalities than others. As dietary exposure is modifiable, one may speculate pending further investigation about the potential for reduction of stage B HF and later mortality.

Key words: **Diet: Vegetarianism: Heart failure: Stage B heart failure: Left ventricular mass: Diastolic function**

Clinical heart failure (HF) affects about 6 million Americans and results from progression from subclinical cardiac structural and functional abnormalities (stage B HF) to clinical (stage C and D) HF. Left ventricular (LV) diastolic abnormalities predict future clinical HF risk and mortality. Thus, their prevention may potentially reduce the burden of CVD in the community. In the Adventist Health Study-2 (AHS-2) of 96 000 subjects, vegetarianism compared with non-vegetarian diet was associated with a lower BMI and lower risk of diabetes, hypertension and ischaemic heart disease despite similar energetic intakes[1–5].

Hence, we hypothesised that vegetarians may have less LV diastolic abnormality and thus fewer associated symptoms[6,7]. If so, this and similar dietary interventions may, under a causal hypothesis, have potential to reduce HF burden and related complications[8] in the community, as diet is potentially modifiable at both individual and population levels. Secondary hypotheses were that vegetarians may differ in their ventricular dimensions, stroke volume and ejection fraction (EF) when compared with non-vegetarians. The study objectives are to test the corresponding null hypotheses.

Methods

Study population

The target study population was AHS-2 members who were readily contacted, lived within 30 miles of Loma Linda, California and were aged >60 years. The selection was stratified by approximately equal numbers of four dietary types, the two main sexes and race (black and non-black).

Dietary subgroups

Using validated self-reported dietary data[9], subjects were classified into vegan (never or <1/month consumption of meat, fish,

Abbreviations: AHS-2, Adventist Health Study-2; EF, ejection fraction; HF, heart failure; LV, left ventricular.

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dairy products or eggs), lacto-ovo-vegetarians (consumption of meat and fish combined <1/month and dairy products/eggs >1/week), pesco-vegetarians (consumption of meat<1/month, but fish >1/month) and non-vegetarians (meat consumption >1/week).

Exclusion criteria

Subjects with more than mild valvular (grade 1) heart disease, EF <45 %, known self-reported but doctor-diagnosed clinical CHD, other heart disease or where there were prosthetic heart valves *in situ* were excluded.

Clinic procedures and definitions

The subjects were invited for a clinic visit in 2014–2015 where histories of diabetes mellitus, hypertension, coronary artery disease, arrhythmias or valvular heart disease were evaluated. The diagnosis of hypertension required either a doctor diagnosis and treatment within the last year, or where the mean blood pressure as measured in clinic using a standard protocol and measured with an Omron automated sphygmomanometer was ≥140/90 (true for both systolic and diastolic) or systolic average > 150. The averages were from readings 2 and 3 of three (each separated by 5 min). A history of diabetes was self-reported, but this required a 'doctor diagnosis' and treatment within the previous 1 year.

We also measured anthropometrics (height, weight) and blood pressure and collected a completed validated FFQ[9]. Physical activity was evaluated as moderate or vigorous exercise ('vigorous activities, such as brisk walking, jogging, bicycling, etc., long enough or with enough intensity to work up a sweat, get your heart thumping, or get out of breath'), with categories: none, ≤60 min/week and >60 min/week.

Echocardiographic methods and definitions

A complete resting echocardiogram was performed using the GE *Vivid Q* system. Guidelines of the American Society of Echocardiography were used both for image acquisition and measurements[10–12]. Images were obtained with the patient in the left lateral decubitus position from parasternal, apical, subcostal and suprasternal views to obtain all the anatomic and Doppler data.

For the echocardiographic analysis, the LV volume, EF, wall motion, diastolic function grade, LV mass, left and right atrial pressures, mitral annular e' velocity, pulmonary vein flow and left atrial volume and other chamber sizes were assessed based on guidelines of the American Society of Echocardiography[10–12].

The mitral inflow was recorded from apical four-chamber view using pulsed wave Doppler technique with a 2 mm sample placed at the tip of mitral leaflets at sweep speed of 50 mm/s. The mitral annular velocity was recorded from the apical 4-chamber view using pulsed tissue Doppler with 2 mm samples placed on medial and lateral mitral annulus, and the recording was performed at 50 mm/s. The pulmonary vein flow was obtained using colour flow guidance from the apical view with a 2 mm pulsed Doppler sample placed about 5 mm inside the right upper pulmonary vein. Measurements were made on three consecutive beats, and the average was taken for each of the subjects. The e' velocities from medial and lateral sides of the mitral annulus were averaged, and the mean e' was used. An E/e' ratio of ≥15 predicts high left atrial pressure. Left atrial volume was computed using the biplane Simpson's method[12]. Clinical HF was diagnosed using modified Framingham criteria[13].

Statistical methods

In the statistical analyses, Student's t tests were used to compare continuous and χ^2 tests for categorical variables. Linear regression was used to test associations between dietary type (modelled as 0/1 indicator variables) and the echocardiographic measures, adjusting for age, sex, race and physical activity. The distributions of all echocardiographic measures used as dependent variables were examined, and those with marked positive skew were log-transformed to improve normality for linear regression analyses. For dichotomous end points, multivariable-adjusted prevalences were estimated by logistic regression, prevalence ratios were calculated and bias-adjusted bootstrap CI and P values for these were estimated. Histories of hypertension or BMI were not initially included as covariates in these regressions, but they were later evaluated as possible mediators between diet and echocardiographic end points. A dozen or so specific food items and histories of cigarette smoking and alcohol consumption were each added to the base model one at a time, to evaluate whether they provided additional explanatory information beyond the dietary pattern variable. The resulting multiple testing was handled by evaluating false discovery using the Benjamini–Hochberg method[14]. Mediation analyses used methods described by VanderWeele[15]. Using the bias-adjusted bootstrap method, 95 % CI for mediation results were calculated [16]. Analyses used R software version 1.1.383. A type 1 error of 0·05 was used to signify statistical significance.

Results

The initial study population was 234 AHS-2 members who were readily contacted, lived within 30 miles of Loma Linda, California and were aged >60 years. Of these, 224 agreed to receive a clinic appointment and 204 attended clinic. However, seventy-one were subsequently excluded according to the exclusion criteria, resulting in 133 analytic subjects. This was to avoid confounding between effects of disorders that were excluded and diet. For some analyses, the dietary groups were collapsed to two main groups: vegetarians (n 95) *v.* non-vegetarians (n 38).

Baseline characteristics of the study subjects are shown in Table 1. The mean age (median, minimum, maximum) of the study sample was 72·7 ((SD 8·7), 67·4, 52·4, 87·7) years, 48 % were females and 32 % African American. The mean left ventricular ejection fraction was 69 (SD 6·4). There were very little or no missing data, with the exception of that for ventricular volumes and hence stroke volume index (35 % missing). This is expected due to frequent inadequate image quality for some necessary measures using echocardiography.

Vegetarians were more likely to be non-African American than were non-vegetarians (75 % *v.*47 %, $P < 0{\cdot}005$). They, when compared with non-vegetarians, had a lower body weight (71·3 (SD 16·2) kg *v.* 80·3 (SD 15·1) kg, $P < 0{\cdot}005$) and lower body

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Table 1. Baseline characteristics of the study subjects by dietary pattern (Mean values and standard deviations; numbers and percentages)

	Vegetarian (*n* 95)			Non-vegetarian (*n* 38)			
	Mean	SD	# missing	Mean	SD	# missing	*P**
Age (years)	72·7	8·8	0	72·6	8·6	0	0·97
	n	%		*n*	%		
Sex (female)	44	46	0	20	53	0	0·52
Race (white)	71	75	0	19	50	0	0·006
	Mean	SD		Mean	SD		
BMI (kg/m^2)	25·6	4·62	1	28·6	5·16	1	0·003
BSA (m^2)	1·81	0·22	1	1·92	0·24	1	0·012
Body weight (kg)	71·3	16·2	0	80·3	15·1	0	0·0049
Vigorous physical activity							0·35
	%			%			
Level 1 (None)	9·8		3	11·1		2	
Level 2 (1–60 min/week)	29·3			41·7			
Level 3 (>60 min/week)	60·9			47·2			
	n	%		*n*	%		
Diabetes	16	17	0	3	8	0	0·29
Coronary artery disease	1	1	0	3	8	0	0·13
Hypertension	47	47	0	24	63	0	0·10
HF history	2	2	0	0	0	0	0·91
Echocardiographic variables							
	Mean	SD		Mean	SD		
Mean heart rate	62·0	9·6	6	64·1	10·0	0	0·26
Ventricular septum (mm)†	10·0	2·2	0	10·27	2·2	0	0·47
Posterior wall (mm)†	8·9	1·9	0	9·4	2·0	0	0·19
Left ventricular mass index	73·6	21·1	1	69·5	19·2	1	0·29
Left ventricular end-diastolic dimension (mm)	42·4	5·7	0	41·4	6·1	0	0·35
Left ventricular end-systolic dimension (mm)	28·0	6·4	0	27·9	6·1	0	0·95
Left ventricular end-diastolic volume index (cc/m^2)	48·3	12·9	29	40·2	11·0	18	0·0084
Left ventricular end-systolic volume index (cc/m^2)	16·1	6·5	29	13·2	6·8	18	0·096
Stroke volume index (cc/m^2)	32·2	7·0	29	27·0	8·6	18	0·0088
Left atrial size (mm)	35·2	6·6	0	35·3	6·6	0	0·90
Left atrial volume (cc)	49·5	20·6	2	50·1	20·5	1	0·88
Left atrial volume index (cc/m^2)	27·4	10·8	2	25·4	9·5	1	0·31
LV ejection Fraction %	69	6·4	0	69	6·4	0	0·82
E velocity (cm/s)	65·0	14·8	0	61·8	16·0	0	0·30
A velocity (cm/s)	73·1	21·4	0	72·1	15·5	0	0·77
Lateral e' (cm/s)	8·1	2·4	0	7·3	2·6	0	0·10
Medial e'(cm/s)	6·6	2·0	0	5·7	1·7	0	0·015
Average e'(cm/s)	7·4	2·1	0	6·5	2·0	0	0·034
E/A velocity ratio	0·95	0·32	0	0·88	0·23	0	0·14
E/e' ratio	9·8	5·2	0	10·3	4·1	0	0·54

BSA, body surface area; CHF, congestive heart failure; LV, left ventricle; E, mid-diastolic mitral flow velocity; A, late-diastolic (atrial) mitral flow velocity; e', mitral tissue velocity.
* *P* values from Student's *t* test for continuous variables and χ^2 tests for categorical variables.
† Adjusted for differences in sex.

surface area (1·81 (SD 0·22) m^2 *v.* 1·92 (SD 0·24) m^2, $P=0·012$), tended towards more vigorous physical activity (NS) and had lower prevalence of hypertension (47 % *v.* 63 %, $P=0·10$) despite similar ages, although not statistically significant in this small dataset. In unadjusted analyses, vegetarians, when compared with non-vegetarians, had higher medial, lateral and average tissue (e') velocities, and also larger average end-diastolic LV volumes (see Table 1).

After adjusting for age, sex, physical activity and race (Table 2), the vegetarian diet was again associated with higher average mitral annular e' velocity (7·44 *v.* 6·48, $P=0·011$), medial mitral annular e' velocity (6·62 *v.* 5·74 cm/s, $P=0·017$) and lateral mitral annular e' velocity (8·25 *v.* 7·22 cm/s, $P=0·019$), also suggesting better LV relaxation processes. However, EF were similar between vegetarians and non-vegetarians.

Similar multivariable-adjusted analyses (Table 3) allowed comparisons of the different vegetarian dietary patterns with non-vegetarians. Broadly, similar findings resulted but with clear trends of greatest differences between vegans and non-vegetarians and similar but less pronounced differences when comparing lacto-ovo-vegetarians with non-vegetarians. Variables measuring diastolic relaxation were more favourable in vegans compared with non-vegetarians, medial e' 6·81 compared with 5·75 cm/s ($P=0·019$), lateral e' 8·51 compared with 7·22 cm/s ($P=0·018$) and average e' 7·66 compared with 6·48 cm/s ($P=0·011$).

Compared with non-vegetarians, vegans had significantly higher values of mid-diastolic mitral flow (E) velocity, clearly higher values of ratio of mid-diastolic to late (atrial) mitral flow velocities (E/A) and possibly much larger values of left

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Table 2. Covariate-adjusted differences (vegetarian–non-vegetarian) as expressed by β-coefficient linear regression*
(Mean values and 95 % confidence intervals)

Echo variable	Vegetarians, mean (*n* 95)†	95 % CI	Non-vegetarians, mean (*n* 38)†	95 % CI	*P*‡
Ventricular septum (mm)	10·0	9·64, 10·5	10·0	9·62, 10·4	0·98
Posterior wall (mm)	8·71	8·37, 9·07	8·90	8·551, 9·27	0·60
Left ventricular mass index (g/m^2)	71·0	67·1, 75·2	64·7	61·1, 68·4	0·10
Left ventricular end-diastolic dimension (mm)	42·3	41·1, 43·4	41·6	40·4, 42·7	0·55
Left ventricular end-systolic dimension (mm)	26·9	25·8, 28·2	28·0	26·8, 29·3	0·40
Left ventricular end-diastolic volume index (cc/m^2)	47·7	44·8, 50·5	43·2	40·4, 46·1	0·17
Left ventricular end-systolic volume index (cc/m^2)	15·7	14·2, 17·2	14·5	13·0, 16·0	0·50
Stroke Volume Index (cc/m^2)	32·0	30·0, 33·9	28·7	26·8, 30·6	0·15
Left atrial volume (cc)	45·5	42·0, 49·4	45·8	42·2, 49·7	0·94
Left atrial volume index (cc/m^2)	25·4	23·5, 27·4	23·6	21·8, 25·5	0·34
Visual ejection fraction (%)	69	67, 70	68	67, 70	0·79
E velocity (cm/s)	65·3	62·3, 68·3	60·4	57·4, 63·4	0·096
A velocity (cm/s)	72·7	69·1, 76·4	71·2	67·5, 74·8	0·67
Lateral e' (cm/s)	8·25	7·81, 8·70	7·22	6·77, 7·66	0·019
Medial e'(cm/s)	6·62	6·26, 6·99	5·74	5·38, 6·11	0·017
Average e'(cm/s)	7·44	7·06, 7·81	6·48	6·10, 6·85	0·011
E/A velocity ratio	0·91	0·86, 0·97	0·84	0·80, 0·89	0·16
E/e' ratio	8·92	8·31, 9·59	9·46	8·81, 10·2	0·41
Mean heart rate/min	62·4	60·3, 64·5	63·6	61·5, 65·7	0·56

E, mid-diastolic mitral flow velocity; A, late-diastolic (atrial) mitral flow velocity; e', mitral tissue velocity.
* Adjusted to covariates that take mean values: age = 72·7 years, sex = 48·1 % female; race = 33·1 % black; exercise = 2·5 (between categories 2 and 3).
† Before any exclusions (see Table 1).
‡ *P* values test difference between vegan and non-vegetarian diets.

ventricular end-diastolic volume index and stroke volume index (although there were more missing data for these variables – see Table 1). Tests of the null hypotheses that mean values of these last variables did not differ across all dietary patterns were statistically significant (except for E). Hence, these hypotheses were rejected E/A ($P = 0{\cdot}020$), left ventricular end-diastolic volume index ($P = 0{\cdot}027$) and stroke volume index ($P = 0{\cdot}047$).

Evaluation of histories of cigarette smoking, alcohol consumption, intakes of total sugar, added sugar, whole grains, refined grains, fruits, vegetables, nuts/seeds, legumes, sodas, other sweets and total energy, in no case, found significant evidence that these variables provided additional explanatory information beyond that of the dietary pattern.

It was of interest to assess whether hypertension, diabetes mellitus or BMI could possibly mediate the apparent effect of diet on the echo variables (Table 4). This evaluation must be tentative in a cross-sectional study. With only nineteen diabetics, however, this variable could not be reliably assessed as a mediator. The table presents estimates of direct and indirect 'effects', adjusting for covariates and allowing for interactions between diet and the potential mediator. Significant indirect 'effects' indicate that the diet may at least in part act on the echo variable through the downstream effect of the mediating variable. Direct effects are residual effects of diet not explained by this mediator.

Significant results ($\alpha = 0{\cdot}05$) for indirect 'effects' are indicated by a dagger when the 95 % CI excludes zero. For all of lateral mitral tissue (e'), medial e', average e' velocities, log (mitral mid-diastolic to atrial flow velocities (E/A) ratio) and log (E/ e' ratio), the lower frequency of hypertension in vegetarians may mediate at least a portion of these dietary effects. These same variables showed similar significant indirect 'effects' indicating that the average lower BMI values in vegetarians may mediate a portion of the dietary effects. However, as hypertension and BMI are related one could also consider a joint mediation 'effect'.

Discussion

This pilot study indicates that a vegan diet is independently associated with better diastolic function based on key diastolic parameters, independent of age, sex and race. Vegans also have higher mitral annular velocities and higher values for the ratio of mid-diastolic to end-diastolic mitral flow velocities. This suggests better diastolic relaxation and hence better diastolic function. Lacto-ovo vegetarians trended in the same direction. Our analyses suggest that, if causal, mediators of these statistical effects of diet may include hypertension and obesity.

Although initial abnormalities in diastolic parameters, including a drop in E/A ratio to less than 1 or an elevation of E/e', will often have little immediate significance in the clinical setting, a proportion of such subjects will already develop raised LV filling pressures with moderate exertion, which is often associated with abnormal breathlessness[6,7]. Further, a larger study from Cleveland clinic of low risk adults demonstrated that diastolic abnormalities (predominantly E/A ratio <1 and higher E/e') were importantly predictive of future mortality[8]. Whether this was independent of common coexisting variables is not clear. The lack of prediction of mortality from mildly abnormal diastolic parameters in another study[17] is less easy to interpret, as by covariate adjustment, the hazard ratios were estimated in the context of both normal and abnormal diastolic function groups being adjusted to estimate effects when values of possible mediating variables such as blood pressure, obesity and diabetes were similar. It is unclear whether mildly abnormal

Table 3. Covariate-adjusted* predicted mean values by diet group (95 % confidence intervals)

Echo variable	Vegan mean (*n* 32)	95 % CI	Vegan *P*†	LO mean (*n* 31)	95 % CI	LO *P*†	Pesco mean (*n* 32)	95 % CI	Pesco *P*†	NV mean (*n* 38)	95 % CI	Overall *P*‡
Ventricular septum (mm)	9·92	9·25, 10·64	0·84	10·2	9·50, 10·95	0·88	10·0	9·31, 10·7	0·99	10·0	9·34, 10·7	0·97
Posterior wall (mm)	8·80	8·21, 9·44	0·83	8·64	8·05, 9·27	0·56	8·69	8·09, 9·33	0·64	8·90	8·33, 9·51	0·93
Left ventricular mass index (g/m^2)	70·8	64·3, 78·0	0·20	73·7	66·7, 81·4	0·067	68·8	62·4, 75·9	0·39	64·7	58·9, 71·0	0·31
Left ventricular end-diastolic dimension (mm)	41·6	39·6, 43·6	0·99	43·3	41·3, 45·3	0·24	41·9	39·9, 43·9	0·81	41·6	39·7, 43·5	0·60
Left ventricular end systolic dimension (mm)	27·1	25·1, 29·3	0·58	27·0	25·0, 29·2	0·50	26·7	24·7, 28·9	0·42	28·0	26·0, 30·1	0·85
Left ventricular end-diastolic volume index (cc/m^2)	52·5	48·0, 57·0	0·0014	42·8	38·2 , 47·4	0·88	47·5	42·5, 52·5	0·27	43·4	38·0, 48·8	0·027
Left ventricular end-systolic volume index (cc/m^2)	17·7	15·2, 20·2	0·12	13·9	11·4, 16·4	0·73	15·4	12·7, 18·1	0·67	14·6	11·7, 17·6	0·19
Stroke volume index (cc/m^2)	34·8	31·7, 37·9	0·018	28·9	25·7, 32·1	0·96	32·1	28·6, 35·6	0·21	28·8	25·1, 32·5	0·047
Left atrial volume (cc)	44·0	38·3, 50·6	0·69	44·1	38·3, 50·8	0·72	48·8	42·3, 56·3	0·53	45·8	40·1, 52·3	0·72
Left atrial volume index cc/m^2)	25·2	22·1, 28·7	0·48	24·3	21·2, 27·8	0·75	26·8	23·4, 30·7	0·18	23·6	20·8, 26·8	0·57
Visual ejection fraction (%)	68	65·4, 70·0	0·69	69	67·0, 71·6	0·57	69	66·8, 71·4	0·63	68	66·1, 70·5	0·75
E velocity (cm/s)	68·6	63·5, 73·7	0·025	65·0	59·9, 70·2	0·21	62·3	57·1, 67·5	0·61	60·4	55·6, 65·2	0·14
A velocity (cm/s)	70·2	63·9, 76·5	0·85	71·7	65·3, 78·1	0·89	76·3	69·9, 82·7	0·25	71·7	65·1, 77·1	0·55
Lateral e' (cm/s)	8·51	7·75, 9·27	0·018	8·11	7·34, 8·88	0·10	8·13	7·36, 8·91	0·10	7·22	6·50, 7·94	0·11
Medial e' (cm/s)	6·81	6·18, 7·44	0·019	6·60	5·96, 7·24	0·059	6·45	5·81, 7·09	0·12	5·75	5·15, 6·35	0·10
Average e' (cm/s)	7·66	7·01, 8·31	0·011	7·36	6·71, 8·01	0·059	7·29	6·63, 7·95	0·085	6·48	5·87, 7·09	0·075
E /A ratio	1·02	0·925, 1·12	0·0079	0·908	0·823, 1·00	0·30	0·826	0·748, 0·912	0·75	0·844	0·770, 0·926	0·020
E/e' ratio	9·54	8·27, 10·59	0·90	8·86	7·82, 10·0	0·45	8·56	7·55, 9·70	0·26	9·47	8·42, 10·7	0·63
Mean heart rate	61·7	58·0, 65·4	0·45	62·6	59·0, 66·2	0·69	63·0	59·3, 66·7	0·83	63·6	60·3, 66·9	0·89

LO, lacto-ovo-vegetarian; Pesco, pesco-vegetarian; NV, non-vegetarian; E, mid-diastolic mitral flow velocity; A, late-diastolic (atrial) mitral flow velocity; e', mitral tissue velocity.

* Adjusted to covariates that take mean values: age = 72·7 years, sex = 48·1 % female; race = 33·1 % black; exercise category = 2·5 (between categories 2 and 3). Echo measures involving ventricular volume measures had 1/3 less cases in all groups, resulting from technically difficult echocardiograms.

† *P* values test difference from the reference diet (NV).

‡ Overall *P* value tests hypothesis of no difference between diets.

Table 4. Evaluation of hypertension and BMI as possible mediators of the dietary (vegetarian/non-vegetarian) effects*,† (95 % confidence intervals)

Echo variable	E velocity (cm/s)	A velocity (cm/s)	Lateral 'e (cm/s)	Medial e' (cm/s)	Average e' (cm/s)	Log (E/A ratio)	Log (E/e ratio)	Stroke vol index (cc/m^2)	EDVI (cc/m^2)
A. Possible mediator is hypertension									
Direct effects	4·10	3·10	0·65	0·54	0·59	0·056	−0·0022	3·80	5·40
Lower 95 % CI	−4·20	−6·00	−0·46	−0·36	−0·31	−0·091	−0·16	−1·40	−1·80
Upper 95 % CI	13·0	13·0	1·60	1·40	1·40	0·21	0·16	9·30	12·0
Indirect effects	−1·40	−5·30	0·32†	0·36†	0·34†	0·048†	−0·073†	0·36	0·40
Lower 95 % CI	−5·20	−13·0	0·0009	0·016	0·010	0·0012	−0·18	−0·41	−0·80
Upper 95 % CI	0·21	0·0083	0·91	0·91	0·88	0·13	−0·0041	0·042	8·90
B. Possible mediator is BMI									
Direct effects	4·10†	3·00	0·67	0·55†	0·61†	0·058	−0·0039	3·80	5·30
Lower 95 % CI	−3·70	−5·90	−0·45	−0·30	−0·30	−0·085	−0·16	−1·10	−1·10
Upper 95 % CI	13·0	12·0	1·70	1·30	1·40	0·20	0·16	9·30	12·0
Indirect effects	−1·30	−4·70†	0·29†	0·32†	0·30†	0·043†	−0·065†	0·32	0·36
Lower 95 % CI	−4·50	−12·0	0·023	0·034	0·033	0·0046	−0·17	−0·25	−0·52
Upper 95 % CI	0·11	−0·42	0·85	0·84	0·83	0·12	−0·0085	0·022	0·0013

E, mid-diastolic mitral flow velocity; A, late-diastolic (atrial) mitral flow velocity; e', mitral tissue velocity; EDVI, end-diastolic left ventricular volume index).
* Bias-corrected bootstrap 95 % confidence intervals.
† Numbers identify significant mediation (indirect effects where the confidence interval excludes 0).

diastolic parameters themselves may be causal factors for increased mortality, or rather are just markers of that.

Doppler tissue imaging can measure mitral or tricuspid annulus velocities to assess ventricular function in the long axis[18]. Studies have shown that the early mitral annulus velocity (e') provides a relatively preload-independent assessment of LV relaxation[19,20], and the ratio of peak early diastolic mitral inflow velocity (E) over the myocardial annular velocity (e') can be used to estimate LV filling pressure[19–22]. In our study, this measure did not differ according to dietary pattern, indicating similar filling pressures at rest. Tissue Doppler imaging enables measurement of regional and global myocardial systolic and diastolic velocities. The velocities derived from the annulus or LV base primarily reflect longitudinal motion of longitudinally directed fibres, which are found in the sub-endocardium[23]. The e' appears to be a good indicator of diastolic function and correlates well with the time constant of isovolumic relaxation (Tau)[18,24,25]. Nagueh *et al.* also demonstrated that load increases raised the transmitral E velocity by 70 % on average, whereas the same manipulations produced only a 13 % change in mitral tissue velocities (e'). Therefore, low e' values indicate abnormal LV relaxation even when LV filling pressures are increased[26].

However, age does affect tissue Doppler variables, especially e'[27], and also by decreasing early mitral inflow (E) and the ratio early mitral inflow to atrial mitral inflow velocities (E/A)[28]. Studies of Adventists have often focused on healthy ageing. It has been demonstrated that Adventists, particularly vegetarian Adventists, do experience greater longevity[29,30], lower rates of hypertension and ischaemic heart disease[3–5]. The concordance of the observed trends towards better diastolic function in vegetarian Adventists with other pathologies known to affect diastology suggests possible mechanisms underlying these trends.

Recently, E/Vp (velocity of propagation) and E/e' have been reported as good non-invasive correlates of pulmonary capillary wedge pressure[31] and LV filling pressure[21,22]. Moller *et al.* found E/e' and E/Vp to be powerful predictors of composite end point of cardiac death and readmission due to HF after a first myocardial infarction during a median follow-up of 13 months[32].

Data from vegetarians in this study raised the possibility that vegans had higher ventricular volumes and stroke volumes despite similar transverse dimensions and EF (Table 3). Larger ventricular volumes may therefore be due to increase in longitudinal dimension, resulting in a less spherical LV which translates to better relaxation and filling mechanics of left ventricles with similar EF. However, the limitations of echocardiographic imaging prevented strong conclusions regarding ventricular shape differences in this study, as for some of these variables there were substantial missing data. Unfortunately, the subjects with and without missing ventricular volume data (35 %) differed, in that those with missing data were older, were more likely to be hypertensive and had higher values for left ventricular mass index. This limits our ability to clearly associate these measures with diet. Thus, these hypothesis-generating results can be pursued with alternative imaging technologies.

The work of others also suggests that dietary interventions may favourably alter the course of some of the echo measures described above and also the risk of HF and its prognosis. De Simone *et al.* have shown that LV mass increases with a diet high in fat and Na[33]. Diets tending towards either a more vegetarian or a more Mediterranean diet pattern appear to be beneficial for various aspects of HF including survival[34,35]. The Women's Health Initiative found that a Mediterranean diet as well as the DASH diet lowered mortality among women who had previously been hospitalised for HF[36]. The Physicians Health Study-1 reported an increased risk of HF with increasing consumption of red meat[34] and others report that higher intake of carnitine is associated with worsening of aspects of HF including prognosis[35] and contractile function as shown by Diaz *et al.*[37] Dietary characteristics such as meal skipping, meal frequency and interventions such as intermittent fasting are well known to have effects on cardiovascular risk factors such as insulin sensitivity, blood pressure, blood lipids and

hence the metabolic syndrome[38,39]. Further, an intensive cardiac rehabilitation experience, prominently including a plant-based diet, has recently shown an improved metabolic profile and improved survival in patients with CVD[40].

Plasma L-carnitine (present in meat) and its derivatives may be related to development and progression of chronic HF[34,35,41,42]. However, the exact relationship is unclear. Nuts and *n*-3 fatty acids, on the other hand, seem to have a protective effect on incident and fatal coronary events[43,44], HF-free survival[45], incident HF[46] and mortality[36]. The role of soya in the genesis of HF is unclear as few cohorts have sufficient variation in soya intake to assess this. Animal studies suggest a beneficial effect on various parameters including cardiac dysfunction[47], interstitial fibrosis[47] and oxidative stress in a heart model[48] also reduced pulmonary hypertension and right HF[49].

It is important in epidemiological work to consider possible mechanisms whereby an exposure, such as diet, may induce an effect on health. It has long been known that plant-based diets are associated with both lower blood pressure levels and lower BMI values. Both of these are well-known risk factors for CVD[50–52]. Our mediation analyses suggest that some combination of these factors could play a part in any pathophysiology that results from the choice of a less plant-based diet.

There are both strengths and limitations to this work. The AHS-2 cohort is well-characterised, with a very large range of several dietary exposures (meat, dairy products, nuts, fruits/vegetables, *n*-3 fatty acids and soya), which provides a rare opportunity to evaluate dietary relationships to HF. Other work from the AHS-2[2–4] shows that a vegetarian diet is independently associated with lower HF risk factors and, now we report here, evidence also suggesting better diastolic function.

A limitation is that this is a pilot study comprised of a small number of subjects drawn from the much larger AHS-2 cohort. The inability to find specific foods that may partially explain the diet pattern association was probably impeded by a lack of power for this more detailed evaluation. Our population belongs to a specific religious group, although their physiological and metabolic responses to diet are similar to those of other Americans as far as is known. This is a cross-sectional study, where some measured associations may suggest causal hypotheses for further investigation in prospective studies.

It is also important to point out that we focus on E/A ratio, tissue Doppler velocity e', as well as E/e' as diastolic parameters because they are commonly utilised echocardiographic parameters of diastolic function. We do not classify patients into grades of diastolic dysfunction, as grading criteria are not universally accepted, have changed significantly over time[53] and continue to remain in flux[54]. Diastolic grading has not retained diagnostic prominence in clinical trials and is not part of the diagnostic algorithm for HFpEF in the recent internationally endorsed universal definition of HF criteria[55]. On the contrary, individual diastolic parameters such as E/e' continue to be recognised as key markers of structural cardiac abnormalities, as they define a population at risk for HF (also termed stage B or pre-HF)[55]. Therefore, we chose to focus on individual diastolic parameters rather than assigning grades which may vary depending on evolving criteria. This approach retains clinical utility to diagnose stage B HF without more complex diastolic grading.

In summary, our study suggests that vegetarians, especially vegans, have a lower prevalence of LV diastolic abnormalities, as the corresponding null hypotheses are rejected. This provides new evidence about a potential cardiac structural mechanism whereby diet may change risk, and that this could be at least partially mediated by a combination of less hypertension and obesity. Thus, vegetarians appear to experience lower risk of stage B HF and, one could speculate that thereby, less progression and future mortality.

Future prospective research, using echocardiographic and other imaging strategies, with larger study populations will provide more evidence of causality to these associations. Long-term randomised trials of vegetarian diets seem infeasible at present, so future work will depend on well-conducted observational studies with appropriate covariate adjustment. Metabolomic and gene expression studies[56,57] may add further mechanistic insights.

Acknowledgements

Funding was from a seed grant from Loma Linda University, Division of Cardiology; and a NIH/National Cancer Institute grant (U01CA152939). These funding organisations had no role in the design, analysis or writing of this article.

P. V.: writing (original draft); R. P.; conceptualisation, data curation and writing (review and editing); G. F.: conceptualisation, formal analysis, writing (review and editing), and funding acquisition; D. A.: writing (review and editing); B. J.: data curation and administration; A. M.: formal analysis; P. H.: conceptualisation and resources; B. B.: data curation and administration; L. S. data curation; S. K.: conceptualisation and administration.

There are no conflicts of interest.

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British Journal of Nutrition