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Dietary patterns and components to prevent and treat heart failure: a comprehensive review of human studies

Conor P. Kerley[1,2]*

[1]*Chronic Cardiovascular Disease Management Unit and Heart Failure Unit, St Vincent's Healthcare Group/St Michael's Hospital, County Dublin, Republic of Ireland*
[2]*Heartbeat Trust, Dun Laoghaire, County Dublin, Republic of Ireland*

Abstract

Growing evidence has emerged about the role of dietary patterns and components in heart failure (HF) incidence and severity. The objective here is to provide a comprehensive summary of the current evidence regarding dietary patterns/components and HF. A comprehensive search of online databases was conducted using multiple relevant keywords to identify relevant human studies. The Dietary Approaches to Stop Hypertension (DASH) and Mediterranean diets have consistently been associated with decreased HF incidence and severity. Regarding specific dietary components, fruit, vegetables, legumes and whole grains appear beneficial. Current evidence suggests that red/processed meats, eggs and refined carbohydrates are harmful, while fish, dairy products and poultry remain controversial. However, there is a notable lack of human intervention trials. The existing but limited observational and interventional evidence from human studies suggests that a plant-based dietary pattern high in antioxidants, micronutrients, nitrate and fibre but low in saturated/*trans*-fat and Na may decrease HF incidence/severity. Potential mechanisms include decreased oxidative stress, homocysteine and inflammation but higher antioxidant defence and NO bioavailability and gut microbiome modulation. Randomised, controlled trials are urgently required.

Key words: Heart failure: Diet: Nutrition: Patterns: Nutrients

Introduction

Heart failure (HF) occurs when the heart is unable to pump sufficiently to match blood flow to requirement. Signs and symptoms include shortness of breath, excessive tiredness and leg swelling, resulting in decreased exercise capacity and impaired quality of life.

HF is one of the leading causes of hospitalisation, morbidity and mortality worldwide, and incidence is increasing. Although medical advances have improved HF survival, mortality rates remain high[1], with a 10-year survival rate of about 25 %. Therefore, feasible preventive and treatment measures are of considerable clinical and public health importance, yet few exist. In this context, nutritional modification represents an attractive strategy.

CHD, hypertension, atrial fibrillation, valvular heart disease, excess alcohol use, infection and idiopathic cardiomyopathy represent the most common causes of HF. Hypertension, obesity, dyslipidaemia, insulin resistance/diabetes and systemic inflammation are associated with HF incidence/severity. Nutritional factors are major contributors to these risk factors and to CVD itself[1]. Multiple landmark trials have documented the profound effect of nutritional intake on CVD incidence/severity including the Diet And Reinfarction Trial (DART)[2], Dietary Approaches to Stop Hypertension (DASH)[3] and Prevención con Dieta Mediterránea (PREDIMED)[4].

Lifestyle modifications (exercise, smoking cessation) form the cornerstone of early HF treatment combined with medications (for example, angiotensin-converting enzyme inhibitors, beta blockers, diuretics) as well as implanted devices (for example, pacemakers). Regarding HF, most research efforts have focused on pharmacology and devices, with little attention paid to nutrition[5], limiting the understanding of nutritional factors in HF pathogenesis/treatment[5–7]. However, nutritional modification has a relatively low risk:cost ratio and represents an attractive strategy to reduce HF incidence/severity. Dietary guidelines regarding HF are typically modest and unspecific with a focus on Na and fluid restrictions. However, targeted nutritional modification may have superior effects in HF prevention/treatment. The aim of the present review is to summarise current evidence regarding dietary patterns/components and HF.

Methods

References were identified by searches of MEDLINE, CINAHL, Embase and online Cochrane databases up to October 2017. Table 1 details multiple specific keyword searches used, each in conjunction with 'heart failure'. Only papers published in English were included and their bibliographies were searched for further references.

Abbreviations: AHEI, Alternate Healthy Eating Index; DASH, Dietary Approaches to Stop Hypertension; EVOO, extra-virgin olive oil; HF, heart failure; MedDiet, Mediterranean diet; PBUT, protein-bound uraemic toxins; PREDIMED, Prevención con Dieta Mediterránea; TMAO, trimethylamine *N-oxide*.

* **Corresponding author:** Dr Conor P. Kerley, email conorkerley@gmail.com

Table 1. Keyword searches

Specific to dietary pattern	Specific to dietary components
Diet	Diet(ary) fatty acid
Dietary pattern	Monounsaturated
Nutrition	Polyunsaturated
DASH	Saturated fat
Mediterranean	Trans fat
Low-fat	Dairy
Paleo(lithic)	Milk
	Eggs
	Fish
	Meat
	Poultry
	Starch
	Diet(ary) fiber
	Grain
	Nut
	Soy(a)
	Vegetable
	Fruit
	Nutrient
	Carotenoid
	Flavonoid
	Polyphenol
	Anthocyanin

DASH, Dietary Approaches to Stop Hypertension.

Studies were excluded if they reported solely on pharmaceutical intervention or animal model research. Further, salt/Na or fluid restriction, micronutrient supplementation, alcohol and over-/undernutrition (i.e. obesity or malnutrition/cardiac cachexia) are important and major topics themselves and are outside the scope of the present review. These topics have been omitted as the focus here is on dietary pattern and food components as opposed to individual nutrients. All references specific to HF were included, while references related to CVD in general or non-HF CVD were not included.

Results

Evidence linking specific lifestyles with heart failure

Several epidemiological studies in the last decade have demonstrated an inverse association between healthy lifestyle and decreased HF risk. In these studies, a healthy lifestyle (regular physical activity, healthy dietary pattern, normal BMI, no/moderate alcohol, not smoking) was associated with 45–81 % decreased HF incidence[8–16]. These studies demonstrate that greater adherence to healthy behaviours was associated with a graded reduction in HF incidence (Table 2), suggesting a major role for lifestyle factors, including diet, in primary prevention of HF. Because these studies included several lifestyle factors, the specific effect of nutrition cannot be elucidated.

Additionally, there have been several randomised controlled trials that focused on educational interventions to improve nutritional knowledge and compliance with dietary recommendations in HF. These trials noted increased nutritional knowledge, higher compliance with dietary guidelines, increased exercise tolerance[17] and even decreased HF hospitalisation/death[18]. These educational trials are important because they suggest that nutritional intervention in HF is not only possible but also has broad clinical benefit.

Evidence linking specific dietary patterns with heart failure

Dietary patterns involve complex relationships between components of dietary intake, not just a single nutrient. Overall diet assessment represents a broad picture of food and nutrient consumption and has been suggested to be more predictive of disease risk than individual foods/nutrients[19]. Studies of dietary patterns/components regarding HF incidence/severity are detailed in Tables 2–6, including prospective studies (Table 2), cross-sectional studies (Table 3), longitudinal studies (Table 4), nutritional biomarker studies (Table 5) and nutritional intervention trials (Table 6).

Dietary Approaches to Stop Hypertension (DASH) diet. The DASH diet was designed to prevent and treat hypertension[3,20]. Based on early studies of lower blood pressure in vegetarians, 'the diet design goals were to create patterns that would have the blood pressure lowering benefits of a vegetarian diet, yet contain enough animal products to make them palatable to non-vegetarians'[20]. As such, it is a carbohydrate-rich and low-fat diet that emphasises consumption of fruits, vegetables, whole grains, nuts, fish, poultry and low-fat dairy products, and minimises consumption of red meat, sugar and processed foods.

Tables 3 and 4 detail studies of DASH and HF incidence, and Tables 3, 4 and 6 describe studies of DASH and HF severity. A 2013 systematic review and meta-analysis of observational prospective studies including >144 000 adults reported that a DASH-like diet was associated with significant reductions in CVD incidence, including CHD and stroke (19–21 %) but the greatest risk reduction was against HF (29 %)[21]. Although plausible and consistent, these studies are limited by their observational nature.

However, a preliminary intervention trial was published in 2003[22] with follow-up from the pilot Dietary Approaches to Stop Hypertension in Diastolic Heart Failure (DASH-DHF) study in 2012[23–25] (Table 6). Importantly, all foods were prepared and served under observation by dietitians in a metabolic kitchen in DASH-DHF. This pilot study was conducted among a small group of primarily obese, postmenopausal, women. Further, there was a mean weight loss of 1·7 kg, which may explain most/some benefit. Nevertheless, improvements in cardiac function after 21 d infer a remarkable response. A subsequent randomised, non-blinded trial reported vascular, ergonomic and quality-of-life benefit without weight change[26].

A limitation of both trials is the lack of investigator blinding. Nevertheless, the DASH diet seems promising for preventing and treating HF. Based on consistent evidence of benefit in CVD, including HF, the DASH diet has been called 'an optimal dietary plan for symptomatic HF'[27] and was formally adopted into the 2013 American College of Cardiology/American Heart

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Table 2. Prospective studies of lifestyle and heart failure (HF) risk

Assessment(s)	Mean follow-up	Sample	Age	Outcome(s)	Reference
Six lifestyle factors: Never smoking, PA five or more times/week, Healthy weight, Four fruits and vegetables/d, One or more breakfast cereal/week, Five or fewer alcoholic drinks/week	22·4 years	20 900 Male physicians	40–84 years	50 % Reduced HF incidence with adherence to ≥4 *v.* 0 healthy behaviours. Healthy behaviours were individually and jointly associated with lower lifetime HF risk	Djoussé *et al.* 2009[8]
Five-factor score: BP, Plasma cholesterol, DM, Smoking, Body mass	15–18 years	13 462 White and AA Americans	45–64 years	82 % Reduced HF incidence in those with all optimal risk factors compared with participants with any elevated risk factor using the four-factor score (no body mass). A population attributable fraction estimate suggested that having ≥1 of the five risk factors accounted for 88·8 % of HF events	Folsom *et al.* 2009[9]
Four lifestyle factors: Not currently smoking, Moderate or high PA, Healthy weight, Three or more vegetables/week	14·1 years	38 075 Adults	25–74 years	70 % (Males) and 81 % (females) reduced HF incidence in those who adhered to 4 *v.* 0 healthy behaviours	Wang *et al.* 2011[10]
Five modifiable risk factors: Cigarette smoking, DM, Elevated LDL, HTN, Obesity	17·6 years	14 709 White and AA Americans	45–64 years	All five risk factors were independently associated with elevated HF risk, with the strongest association for DM	Avery *et al.* 2012[11]
Four lifestyle factors: Healthy weight, Regular PA, Moderate alcohol consumption, Not smoking	21·7 years	20 060 Male physicians, including a subset whose parents had MI <55 years	40–84 years	A score '>2' was defined as a 'good lifestyle score' while a score of '≤2' was defined as a 'poor lifestyle score'. Compared with subjects with good lifestyle score and no parental history of premature MI, risk was higher in individuals with either poor lifestyle score or parental history of premature MI but highest in those with both	Khawaja *et al.* 2012[12]
Four lifestyle factors: Not currently smoking, Moderate–vigorous PA, Healthy weight, Healthy diet (AHEI)	11 years	84 537 Adults	50–79 years	77 % Reduced HF incidence in those who adhered to 4 *v.* 0 healthy behaviours	Agha *et al.* 2014[13]
Six lifestyle factors: Not currently smoking, Walking pace ≥2 mph, PA, Healthy weight, One or fewer alcoholic beverages/week, Healthy diet	21·5 years	4990 Adults	72 years (mean)	45 % Reduced HF incidence in those who adhered to ≥4 *v.* <4 behaviours	Del Gobbo *et al.* 2015[14]
'Life's Simple 7': Smoking, BMI, PA, Diet,	22·5 years (median)	13 462 White and AA Americans	45–64 years	73 % Reduced HF incidence in those with 5–7 ideal components compared with those with 0 ideal	Folsom *et al.* 2015[15]

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Table 2. *Continued*

Assessment(s)	Mean follow-up	Sample	Age	Outcome(s)	Reference
Total cholesterol, BP, Fasting serum glucose				components Each component was independently associated with reduced HF incidence	
Four lifestyle factors: Not currently smoking, PA, Healthy body weight, Healthy diet	13 years	64 679 Adults	50·3 years (mean)	62 % (Males) and 72 % (females) reduced HF incidence for those who adhered to all 4 *v.* 0 behaviours. Each healthy lifestyle factor was accumulatively associated with a statistically significant lower HF risk	Larsson *et al.* 2016[16]

AA, African-American; AHEI, Alternative Healthy Eating Index; BP, blood pressure; DM, diabetes mellitus; HTN, hypertension; MI, myocardial infarction; mph, miles per h, PA, physical activity.

Association CVD risk prevention guidelines (strong recommendation: 2013: level 1A)[28].

Mediterranean diet. Dietary patterns in the Mediterranean region are often characterised by a high intake of vegetables, fruits, nuts, whole grains and extra-virgin olive oil (EVOO) with a moderate intake of fish and sometimes wine (with meals), and a low intake of dairy products, poultry, red/processed meats and free sugars[29].

One of the first reports of the Mediterranean diet (MedDiet) was published in 1996 from the Lyon Diet Heart Study. This was a randomised, single-blind trial to test the hypothesis that a MedDiet would reduce CVD complications in survivors of a first acute myocardial infarction. In the usual-care group, there were eight cases of non-fatal HF in 303 subjects (1·35 %), while there were two cases in 302 subjects following a MedDiet (0·33 %) after 27 months[30]. An extended follow-up of this study demonstrated that the MedDiet significantly reduced the risk of a composite endpoint that included HF by 67 % ($P = 0·0001$)[31]. These preliminary observations were followed by several cross-sectional and prospective studies (Tables 2–6).

There is only a single randomised, controlled trial assessing primary prevention of HF with the MedDiet[32]. This was a secondary analysis of the PREDIMED trial, which differs from the Lyon Heart study in that it compares a MedDiet supplemented with either EVOO or nuts with a low-fat diet. PREDIMED involved 7403 adults and 6·8 years of follow-up. Although there was no protective association of the MedDiet (with EVOO or nuts) on HF incidence, HF incidence was 22–32 % lower in point estimates throughout the trial for the MedDiet + EVOO intervention. Further exploratory analysis regarding a composite outcome of total CVD events (including HF) demonstrated 38 and 23 % reduced HF incidence associated with the MedDiet + EVOO and MedDiet + nuts interventions. The lack of protective effect may be partially explained by the low HF incidence, short follow-up and the moderate–high baseline adherence to the MedDiet[32]. A 2016 systematic review and meta-analysis involving 10 950 participants comparing randomised controlled trials of Mediterranean with control diets suggested that the MedDiet was associated with a 70 % decreased HF incidence[33].

There are currently no intervention studies of the MedDiet in HF. However, a 2008 report based on a controlled, clinical trial of the MedDiet *v.* a low-fat diet *v.* usual care noted improved event-free survival with both the MedDiet (84 %) and low-fat diet (84 %) than usual-care controls (60 %) (log-rank $P < 0·001$). It is noteworthy that both diets were low in saturated fat (≤7 % energy) and dietary cholesterol (≤200 mg/d)[34]. Further, a 2014 biochemical analysis of the PREDIMED trial suggested that the MedDiet could decrease important HF biomarkers, even in the absence of weight loss[35].

Dietary Approaches to Stop Hypertension (DASH) v. Mediterranean diet. Both patterns are largely plant-based, centred on fruits, vegetables and whole grains and low in red/processed meat and refined carbohydrates. A 2013 prospective study explored the effect of Mediterranean and DASH diet scores on mortality rates in women with pre-existing HF (n 3215; aged 50–79 years). The highest *v.* lowest diet score for the DASH diet was associated with 16 % significantly lower mortality (P trend = 0·01) and a trend towards 15 % reduced mortality with the MedDiet (P trend = 0·08)[36]. A 16 % mortality reduction after HF hospitalisation eclipses any currently available or previously investigated therapy[7].

The Rice Diet. In 2014, two articles recounted Dr Walter Kempner and his 'Rice Diet'[37,38]. The Rice Diet Program was founded in 1939 and the diet consisted of white rice, sugar, fruit, fruit juices, supplemental Fe and vitamins (including thiamine) and provided about 2000 kcal (8370 kJ), 20 g protein, about 2–3 % fat, 1000 ml liquid and 150–250 mg Na daily. Blood pressure and related symptoms reportedly began to decline rapidly. If results were good, after several months small amounts of lean meat and vegetables were added. A 1949 editorial stated 'Kempner's own therapeutic results are little short of miraculous…practically speaking, there is probably no more effective diet for obese decompensated cardiac patients'[39].

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Table 3. Cross-sectional studies of dietary patterns/food and heart failure (HF) outcome

Assessment(s)	Sample	Age	Outcome(s)	Reference
Dietary patterns				
MedDiet	372 Consecutive HF patients	Not reported	The MedDiet score was positively correlated with log-Smv, left atrial EF and V(p), but inversely correlated with log-E:A and log-Emv/Amv levels ($P<0·05$). After adjusting for potential confounders, only log-E:A remained significant ($P<0·05$)	Chrysohoou *et al.* 2010[73]
DASH	6814 Ethnically diverse adults without CVD	45–84 years	Greater consistency with DASH diet was associated with favourable end-diastolic volume, SV and EF, after adjustment for potential confounders. A one-unit increase in DASH score was associated with a 0·26 ml increase in end-diastolic volume, 0·10 ml/m^2 increase in SV, and a non-significant 0·04 % increase in left-ventricular EF ($P=0·08$)	Nguyen *et al.* 2012[122]
Dietary habits	312 Subjects with advanced HF, awaiting heart transplantation	53 years (mean)	Reduced intake of foods high in SFA and frequent consumption of F&V were related to impaired physical QoL. *Post hoc* analyses revealed that this association only held for overweight/obese patients	Bunyamin *et al.* 2013[55]
Dietary Inflammatory Index	15 693 Adults	Not reported	Subjects in DII quartile 4 were 30 % more likely to have a previous circulatory disorder (including HF) compared with quartile 1	Wirth *et al.* 2016[59]
Dietary components				
Dairy products	86 Adults	70·4 years (mean)	Higher intake associated with poorer memory ($P=0·01$) and higher pulsatility index in the medial cerebral artery ($P=0·05$)	Garcia *et al.* 2015[123]
Olive oil	651 Consecutive ACS patients	65·4 years (mean)	65 % Reduced LVSD development in those with exclusive olive oil consumption in multi-adjusted analysis	Chrysohoou *et al.* 2010[74]
Dietary fats	42 Adults	61 years (mean)	TNF-α was elevated in patients with diets higher *v.* lower in either SFA and/or TFA. Patients consuming higher dietary PUFA and especially dietary *n*-3 had lower soluble TNF receptor levels	Lennie *et al.* 2005[94]
Nutrients				
β-Carotene	91 HF subjects	63·2 years (mean)	Significant negative correlation with plasma CRP ($P<0·005$), but not in adjusted analysis. In adjusted analysis, significant negative correlation with plasma MCP-1 ($P<0·001$)	Chung *et al.* 2011[97]
β-Carotene (case–control)	51 HF patients and 31 controls	62 years (mean)	Oxidative stress was higher in HF cases and correlated with HF severity. β-Carotene levels correlated negatively with functional class ($P<0·01$)	Serdar *et al.* 2001[88]
Folate	91 HF subjects	63·2 years (mean)	Significant negative correlation with plasma CRP in adjusted analysis ($P<0·05$), but not adjusted analysis. In adjusted analysis, significant negative correlation with plasma MCP-1 ($P<0·001$) and plasma IL-8 ($P<0·001$). Dietary folate intake was a primary influencing factor on plasma MCP-1 ($P<0·005$) and IL-8 ($P<0·001$) through stepwise multiple linear regression analysis	Chung *et al.* 2011[97]
Vitamin C	91 HF subjects	63·2 years (mean)	Significant negative correlation with plasma CRP in adjusted analysis ($P<0·005$), but not adjusted analysis. In adjusted analysis, significant negative correlation with plasma MCP-1 ($P<0·001$)	Chung *et al.* 2011[97]
Vitamin E (case–control)	51 HF patients and 31 controls	62 years (mean)	Negative correlation between vitamin E level and functional class ($P<0·0001$)	Serdar *et al.* 2001[88]
Multiple micronutrients (case–control)	30 Patients with class II and III NYHA HF and 55 controls	Not reported	Lower plasma vitamin E, lutein, zeaxanthin, cryptoxanthin, lycopene, α-carotene and β-carotene in HF cases compared with controls ($P<0·001$). Class II NYHA patients showed significantly higher levels of vitamin A, vitamin E, lutein and lycopene were significantly higher in class II NYHA patients. EF was directly correlated with vitamin A, vitamin E, lutein and lycopene levels	Polidori *et al.* 2002[89]
Multiple micronutrients (case–control)	30 Patients with class II and III NYHA HF and 30 controls	Not reported	Significantly lower vitamins A, C and E as well as carotenoids in HF patients compared with controls. Levels of vitamins A, C and E as well as carotenoids were inversely correlated with oxidative stress	Polidori *et al.* 2004[90]

ACS, acute coronary syndrome; Amv, mitral velocity A wave; CRP, C-reactive protein; DASH, Dietary Approaches to Stop Hypertension; DII, dietary inflammatory index; E:A, ratio of peak velocity flow in early diastole to peak velocity flow in late diastole; EF, ejection fraction; Emv, mitral velocity E wave; F&V, fruit and vegetables; LVSD, left ventricular systolic dysfunction; MCP-1, monocyte chemoattractant protein-1; MedDiet, Mediterranean diet; NYHA, New York Heart Association; QoL, quality of life; Smv, *skeletal muscle ventricles*; SV, stroke volume; TFA, *trans*-fatty acids; V(p), velocity of flow progression.

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Table 4. Longitudinal studies of dietary patterns/food and heart failure (HF) risk and/or outcome

Assessment(s)	Mean follow-up	Sample	Age	Outcome(s)	Reference
Dietary patterns AHEI	10 years	83 183 Healthy women	50–79 years	52 % Decreased HF risk in highest *v.* lowest AHEI quintile ($P<0·001$). However, after further adjustment, risk reduction was 30 % ($P<0·001$)	Belin *et al.* 2011[58]
AHEI	56 months	31 546 Adults with CVD or T2DM	66·5 years (mean)	28 % Decreased HF risk in highest *v.* lowest AHEI quintile ($P<0·001$). 33 % lower HF risk after adjustment for potential mediators of dietary effects in highest *v.* lowest AHEI quintile	Dehghan *et al.* 2012[57]
DASH	7 years	36 019 Women	48–83 years	37 % Decreased HF risk in highest *v.* lowest AHEI quartile after multivariate adjustment. Greater consistency with the DASH diet was dose-dependently associated with greater decreased HF incidence ($P<0·01$)	Levitan *et al.* 2009[124]
DASH	9 years	38 987 Men	59 years (mean)	22 % Decreased HF risk in highest *v.* lowest AHEI quartile after multivariate adjustment (P for trend = 0·006). Greater consistency with the DASH diet was dose-dependently associated with greater decreases in HF incidence ($P=0·006$)	Levitan *et al.* 2009[125]
DASH	4·6 years	3215 Women with pre-existing HF	73·8 years (mean)	16 % Decreased HF mortality risk in highest *v.* lowest quartile after multivariate adjustment (P for trend = 0·01)	Levitan *et al.* 2013[36]
Dietary habits	338 d	318 Heart transplant candidates	53 years (mean)	Frequent intake of salty foods, which correlated positively with SFA and fluid intake, was associated with a 2·9 increase in high-urgency transplantation. Frequent intake of foods rich in MUFA and PUFA was associated with 51 % reduced risk for HF deterioration/death. Trend towards delisting due to improvement with more frequent consumption of F&V + legumes	Spaderna *et al.* 2013[126]
Dietary habits	5·9 years	201 Women with suspected MI	58·3 years (mean)	64 % Decrease in CVD event risk (including HF) with increased F&V. 13 % decreased risk with increased fibre intake	Rutledge *et al.* 2014[127]
DMI	10 years	83 183 Healthy women	50–79 years	39 % Decreased HF risk in highest compared with lowest DMI quintile ($P<0·001$). However, after further adjustment risk reduction was 9 % ($P=0·045$)	Belin *et al.* 2011[58]
DRS	5 6 months	31 546 Adults with CVD or T2DM	66·5 years (mean)	43 % Decreased HF risk in quintile 5 compared with those in quintile 1 (P for trend <0·001)	Dehghan *et al.* 2012[57]
GI and GL	9 years	36 019 Adults	48–83 years	No significant association between dietary GI or GL and HF events	Levitan *et al.* 2010[128]
Low-fat, plant-based diet (+ exercise, stress management and social support)	3 months	Subjects with CHD (*n* 56) or CHD risk factors (*n* 75)	Not reported	Significant decreases in BMI, LDL, CRP, apoB, angina frequency/severity and physical limitations. Median BNP levels increased significantly ($P<0·001$)	Chainani-Wu *et al.* 2010[47]
MedDiet	2 years	1000 Patients who have had ACS	64 years (mean)	7 % Decreased likelihood of developing LVSD at hospitalisation with greater MedDiet score ($P=0·04$) and 12 % less likelihood of recurrent CVD events ($P=0·04$). Trend towards 10 % decreased risk of cardiac remodelling (i.e. EF <50 %) at 3 months follow-up ($P=0·06$)	Chrysohoou *et al.* 2010[73]
MedDiet	4·6 years	3215 Women with pre-existing HF	73·8 years (mean)	Trend towards 15 % decreased HF mortality risk in highest *v.* lowest quartile after multivariate adjustment (P for trend = 0·06)	Levitan *et al.* 2013[36]
MedDiet + extra virgin olive oil or nuts	1 year	930 Adults at high CVD risk	66·7 years (mean)	Both MedDiets decreased plasma NT-proBNP *v.* control group ($P<0·05$). Both MedDiets decreased oxidised LDL ($P<0·05$). Lipoprotein(a) increased with control diet ($P=0·035$) but not with either MedDiet	Fitó *et al.* 2014[35]
MedDiet	39·9 months	709 Anticoagulated AF patients	Not reported	77·4 and 64·1 % Decreases in HF incidence with high adherence and intermediate adherence compared with low adherence ($P<0·001$). The MedDiet score was dose-dependently inversely correlated with soluble NOX2-derived peptide ($P<0·001$) and F2-isoprostanes ($P<0·001$). MedDiet score predicted CVE in Cox regression analysis ($P=0·001$)	Pastori *et al.* 2015[91]
MedDiet	10 years	32 921 Women	Not reported	21 % Decreased risk in HF risk in highest *v.* lowest quartile of MedDiet score ($P=0·004$)	Tekonidis *et al.* 2015[129]
MedDiet	10·9 years	37 308 Men	59 years (mean)	31 % Decrease in HF incidence for the highest *v.* lowest quartile of MedDiet score. 45 % decrease in HF mortality for the highest *v.* lowest quartile of MedDiet score	Tekonidis *et al.* 2016[130]

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Table 4. *Continued*

Assessment(s)	Mean follow-up	Sample	Age	Outcome(s)	Reference
MedDiet	8·2 years	24 008 Adults	Not reported	24 % Lower HF risk with each 2-unit increment in MedDiet score. After multivariable adjustment, this association was slightly attenuated and lost significance	Wirth *et al.* 2016[75]
Dietary components					
Breakfast cereal (7 servings *v.* 0)	19·6 years	21 376 Male physicians	Not reported	29 % Decreased HF risk after multivariate adjustment. The protective effect was limited to whole grain cereals ($P<0·001$ for trend) and not refined cereals ($P=0·7$ for trend)	Djoussé & Gaziano, 2007[131]
Chocolate	9 years	31 823 Adults	48–83 years	32 % Decreased HF risk for 1–3 servings of chocolate/month compared with no regular intake. However, 9 and 23 % increase for those consuming 1–2 or 3–6 servings/week (P for quadratic trend = 0·0005)	Mostofsky *et al.* 2010[132]
Chocolate	9·3 years	20 278 Adults	66 years (mean)	20 % Decreased HF risk with consumption of 28 g/week *v.* <1/month after multivariate adjustment	Petrone *et al.* 2014[133]
Chocolate	12·5 years	20 922 Adults	58 years (mean)	19 % Decreased HF risk in highest quintile (up to 100 g/d) compared with the lowest. Results were no longer significant after controlling for co-morbidities	Kwok *et al.* 2016[134]
Chocolate	14 years	31 917 Adults	45–79 years	12, 17 and 18 % Decreased HF risk with 1–3 servings/month, 1–2 servings/week, and 3–6 servings/week compared with no chocolate intake. However, 10 % increased risk for those consuming ≥1 serving per d (P for quadratic trend = 0·001)	Steinhaus *et al.* 2017[135]
Dairy products	13·3 years	14 153 White and AA adults	45–64 years	8 % Increased HF risk per one serving high-fat dairy food/d	Nettleton *et al.* 2008[60]
Eggs	20·4 years	21 275	54 years (mean)	28 and 64 % Increased HF risk for egg consumption of 1 per d and ≥2 per d compared with <1 per week in multivariate analysis	Djoussé & Gaziano, 2008[61]
Eggs	13·3 years	14 153 White and AA adults	45–64 years	23 % Increased HF risk per 1 egg/d = 1·23, after multivariable adjustment	Nettleton *et al.* 2008[60]
Eggs	13 years	37 766 Men and 32 805 women	61 years (mean)	30 % Increased HF risk with ≥1 egg/d in men. No association in women, in those with DM or with ≤6 eggs/week	Larsson *et al.* 2015[62]
Fatty acids	14·3 years	3592 Adults	45–64 years	No association	Yamagishi *et al.* 2008[136]
Fatty acids	1 year	118 Adults	52–75 years	33 % Decreased HF mortality risk for PUFA and 15 % increased risk for SFA (both as percentage of daily energy)	Colin-Ramirez *et al.* 2014[137]
Fatty acid: linoleic acid	9 years	36 234 Middle–older women	48–83 years	No significant association with HF risk	Levitan *et al.* 2012[138]
Fatty acid: ALA	6–8 years	4432 Adults	72 years (mean)	No association with incident HF risk	Lemaitre *et al.* 2012[78]
Fish	12 years	4738 Adults	73 years (mean)	31 % Decreased HF risk for fish consumption 3–4 times/week compared with ≤1/month. 32 % deceased HF risk for baked/broiled fish consumption ≥5 times/week *v.* once/month and the trend across the frequency categories was statistically significant (P 0·009). 37 % decreased HF risk in highest quintile of very long-chain *n*-3 fatty acids (EPA and DHA) intake than in the lowest. However, 35 % increased HF risk for fried fish ≥1/week	Mozaffarian *et al.* 2005[139]
Fish	13·3 years	14 153 White and AA adults	45–64 years	No association	Nettleton *et al.* 2008[60]
Fish and *n*-3 fatty acids	12·7 years	57 972 Japanese adults	40–79 years	24 % Decreased HF mortality for highest *v.* lowest quintile of fish intake and 42 % decreased HF mortality for highest *v.* lowest quintile of *n*-3 PUFA intake. Stronger inverse association between fish/*n*-3 PUFA and HF than for other CVD	Yamagishi *et al.* 2008[136]
Fish	11·4 years	5299 Adults	68 years (mean)	11 % Decreased HF risk for highest *v.* lowest quintile of EPA + DHA after multivariate adjustment. This association held for women but not men. No association with fish	Dijkstra *et al.* 2009[140]
Fish	7 years	39 367 Men	45–79 years	Mostly non-significant U-shaped association with fish and *n*-3 consumption. However, 33 % decreased HF risk in third quintile of *n*-3 consumption compared with the first quintile. HF event rates were similar among the highest and lowest fish consumers	Levitan *et al.* 2009[141]
Fish	8 years	36 234 Women	48–83 years	14, 20, 30 and 9 % Decreased HF risk with fish consumption <1 serving/week, 1 serving/week, 2 servings/week and ≥3 servings/week (P for trend – 0·049). 25 % decrease HF risk in highest marine *n*-3 fatty acid quintile compared with lowest	Levitan *et al.* 2010[142]

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Table 4. *Continued*

Assessment(s)	Mean follow-up	Sample	Age	Outcome(s)	Reference
Fish	15 years	4735 Adults	> 65 years	No significant association between fish consumption and HF risk when evaluated with or without adjustment for *n*-3 PUFA	Mozaffarian *et al.* 2011[77]
Fish	10 years	84 493 Women	50–79 years	30 % Decreased HF risk with baked/broiled fish consumption ≥5 servings/week. No protective effect of moderate fish intake (i.e. once/week). 22 % decreased HF risk with consumption of baked/broiled dark fish (for example, salmon, mackerel, bluefish), whereas consumption of baked/broiled white fish (for example, sole, snapper, cod) was not protective and there was 48 % increased HF risk with fried fish consumption ≥1 servings/week. No significant associations between EPA + DHA, ALA, or TFA intake and HF	Belin *et al.* 2011[143]
Fish	14 years	19 097 Adults	58·7 years (mean)	About 30 % decreased HF risk for all categories of fish consumption greater >1/month with the lowest risk in in quintile 3. Trend towards 19 % decreased HF risk in quintile 4 of dietary marine *n*-3 PUFA with a non-linear pattern across quintiles	Wilk *et al.* 2012[144]
Fish	8·2 years	24 008 Middle-aged participants	Not reported	41 % Decreased HF risk in highest *v.* lowest quintile of fish consumption	Wirth *et al.* 2016[75]
Fried foods	9·6 years	15 362 Male physicians	66 years (mean)	103 % Increased HF risk with highest fried food consumption *v.* the lowest (*P* linear trend = 0·0002). Graded increase in HF incidence with increasing fried consumption	Djoussé *et al.* 2015[145]
F&V	13·3 years	14 153 White and AA adults	45–64 years	No associated with HF risk after multivariable adjustment	Nettleton *et al.* 2008[60]
F&V	22·4 years	20 900	40–84 years	15 % Decreased HF risk with vegetables ≥4 *v.* <4 servings/d	Djoussé *et al.* 2009[8]
F&V	14·1 years	38 075 Adults	25–74 years	30 % Decreased HF risk with ≥3 vegetables/week compared with <3/week, but only among men (*P* for trend = 0·047). Fruit was not associated	Wang *et al.* 2011[10]
F&V	12·9 years	34 319	49–83 years	20 % Decreased HF risk in highest *v.* lowest F&V quintile after multivariate adjustment. 17 % decreased HF risk in highest *v.* lowest vegetable consumption (mutually adjusted for fruit) but fruit alone was not associated. Lowest HF rates were in those consuming ≥5 servings/d of F&V (*P* = 0·01). Apples, pears and berries were specific fruits, while green leafy vegetables were specific vegetables inversely associated with HF risk in a dose–response manner	Rautiainen *et al.* 2015[84]
Meat	13·3 years	14 153 White and AA adults	45–64 years	27 % Increased HF risk for every 1 serving/d increase in red meat. However, after multivariable adjustment, there was no association	Nettleton *et al.* 2008[60]
Meat	19·9 years	21 120 Male physicians	54·6 years (mean)	24 % Increased HF in highest *v.* lowest quintile of red meat (*P* for trend = 0·007). There was a positive and graded relationship between red meat consumption and HF	Ashaye *et al.* 2011[85]
Meat	11·8 years	37 035 Men	59·5 years (mean)	28 % Increased HF risk with consumption ≥75 g/d compared with those who consumed <25 g/d (*P* trend = 0·01). 43 % increased HF mortality with consumption ≥75 g/d compared with those who consumed <25 g/d (*P* trend < 0·001) in multivariate analysis. 8 and 38 % increases in HF risk and mortality for each 50 g/d increment in processed meat consumption	Kaluza *et al.* 2014[49]
Meat	13·2 years	34 057 Women	48–83 years	78 % Increased HF risk with consumption ≥50 g/d of processed red meat *v.* <25 g/d. Consumption of unprocessed meat was not associated with increased risk of HF incidence	Kaluza *et al.* 2015[87]
Meat	8·2 years	24 008	Not reported	104 % Increased HF risk for highest *v.* lowest quintile of meat consumption	Wirth *et al.* 2016[75]
Nuts	19·6 years	20 976 Physicians	55 years (mean)	No association	Djoussé *et al.* 2008[119]
Nuts	13·3 years	14 153 White and AA adults	45–64 years	No association after multivariable adjustment	Nettleton *et al.* 2008[60]
Potatoes	13 years	69 313	Not reported	No association	Larsson & Wolk, 2016[146]

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Table 4. *Continued*

Assessment(s)	Mean follow-up	Sample	Age	Outcome(s)	Reference
Sweetened beverages	11·7 years	42 400 Men	45–79 years	23 % Increase in HF risk with consumption of ≥2 servings (200 ml) *v.* non-consumers, after multivariate adjustment (*P* for trend <0·001)	Rahman *et al.* 2015[120]
Tomatoes (retrospective*)	Not reported	Not reported	Not reported	215, 231 and 510 % Increased HF risk with moderate, low and very low tomato consumers compared with high monthly consumption. Tomato consumption was inversely associated with leucocyte count (*P* < 0·05)	Wood & Johnson, 2004[93]
Whole grains	13·3 years	14 153 White and AA adults	45–64 years	7 % Decreased HF risk with each whole grain serving/d, after multivariable adjustment	Nettleton *et al.* 2008[60]
Nutrients					
Antioxidants	11·3 years	33 713	49–83 years	42 % Decreased HF risk in highest quintile *v.* with the lowest (*P* for trend <0·001)	Rautiainen *et al.* 2013[147]
Lycopene	1 year	212 Subjects with pre-existing HF	60 years (mean)	Higher lycopene intake was associated with longer cardiac event-free survival *v.* lower lycopene intake (*P* = 0·003). 201 and 234 % decrease in cardiac event-free survival in the low lycopene intake group with daily Na intakes of >3 g and ≤3 g	Biddle *et al.* 2013[148]
Ca	4·6 years (median)	3340 Women who experienced HF hospitalisation	73·8 years (mean)	Not associated with HF mortality	Levitan *et al.* 2013[149]
Mg	14·7 years (median)	58 615 Healthy adults	40–79 years	50 % Decreased HF mortality (*P* for trend = 0·002)	Zhang *et al.* 2012[150]
Mg	4·6 years (median)	3340 Women who experienced HF hospitalisation	73·8 years (mean)	Not associated with HF mortality	Levitan *et al.* 2013[149]
Mg	5 years	4916 AA adults	55·3 years (mean)	53 % Decreased HF admission in highest Mg/kg quartile compared with lowest but no lowering of HF hospitalisation after the third quartile of Mg intake. Quartiles of Mg intake/kg were also inversely related to Doppler peak mitral E-wave velocity (a surrogate for diastolic function) and tricuspid regurgitation peak velocity (an estimate of pulmonary systolic pressures) but unrelated to systolic function	Taveira *et al.* 2016[151]
Micronutrients	2 years	232 Patients with HF	Not reported	Depressive symptoms conferred greater risk of cardiac events in patients with a high number of micronutrient deficiencies than in those with a low number of micronutrient deficiencies. Patients with a depression score ≥10 and number of micronutrient deficiencies >5 had 2·4 times higher risk for cardiac events compared with patients with a depression score <10 and micronutrient deficiency ≤5 (*P* = 0·005)	Song *et al.* 2015[108]
K	4·6 years (median)	3340 Women who experienced HF hospitalisation	73·8 years (mean)	Not associated with HF mortality	Levitan *et al.* 2013[149]
Vitamin C	11 years	3919 Adults	60–79 years	No association with HF	Wannamethee *et al.* 2013[104]
Vitamin C	2 years	200 HF patients	Not reported	168 % Decrease in cardiac event-free survival with vitamin C deficiency (*P* = 0·029). 140 % increase in odds of hsCRP >3 mg/l with deficient vitamin C intake (*P* = 0·023). The interaction of having hsCRP >3 mg/l and deficient vitamin C intake was associated with a 2·3-fold higher risk for CVE (*P* = 0·002). Higher level of hsCRP predicted shorter cardiac event-free survival, but only in patients with deficient vitamin C intake (*P* = 0·027), not in those with adequate vitamin C intake	Song & Kang, 2018[105]
Vitamin E	11 years	3919 Men	60–79 years	23 % Increased HF risk for each 1 SD after adjustment	Wannamethee *et al.* 2013[104]

AA, African-American; ACS, acute coronary syndrome; AF, atrial fibrillation; AHEI, Alternate Healthy Eating Index; ALA, α-linolenic acid; BNP, brain natriuretic peptide; CRP, C-reactive protein; CVE, cardiovascular events; DASH, Dietary Approaches to Stop Hypertension; DMI, Dietary Modification Index; DRS, Diet Risk Score; EF, ejection fraction; F&V, fruit and vegetables; GI, glycaemic index; GL, glycaemic load; hsCRP, high-sensitivity CRP; LVSD, left ventricular systolic dysfunction; MedDiet, Mediterranean diet; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; T2DM, type 2 diabetes; TFA, *trans*-fatty acids.

* Retrospective study.

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Table 5. Nutritional biomarker studies and heart failure (HF) risk and/outcome*

Assessment(s)	Mean follow-up	Sample	Age	Outcome(s)	Reference
Antioxidants	Cross-sectional	21 HF patients and healthy age- and sex-matched controls	27–76 years	Plasma α-tocopherol (vitamin E) and retinol (vitamin A) were in the normal range. Plasma vitamin C, β-carotene and Se were significantly lower in HF ($P=0{\cdot}005$; 0·01; <0·0005). Plasma Se was strongly correlated with peak VO_2 in univariate and multivariate analyses (both $P=0{\cdot}0005$)	de Lorgeril *et al.* 2001[83]
α-Carotene	17·8 years	1031 Adults	46–65 years	Not related to risk of HF	Karppi *et al.* 2013[76]
β-Carotene	29 years	2321 (259 HF cases)	>50 years	21 % Decreased HF risk for each 1 SD	Ingelsson *et al.* 2005[106]
β-Carotene	17·8 years	1031 Men	46–65 years	308 % Increased HF risk for those in lowest quartile *v.* highest quartile ($P<0{\cdot}001$)	Karppi *et al.* 2013[76]
Lycopene (retrospective)	Not reported	Not reported	Not reported	75 % Decreased HF in those with moderate compared with low serum lycopene ($P<0{\cdot}05$). Inverse dose–response between serum lycopene and CRP ($P<0{\cdot}05$)	Wood & Johnson, 2004[93]
Lycopene	17·8 years	1031 Adults	46–65 years	Not related to HF risk	Karppi *et al.* 2013[76]
Mg	36 months	1569 HF patients with normal sinus rhythm	64 years	11 % Decreased HF mortality with normal compared with low Mg ($P=0{\cdot}024$)	Adamopoulos *et al.* 2009[152]
Mg	21–23 years	14 709 AA and Caucasian adults	45–64 years	71 % Increased HF risk in lowest *v.* highest category of Mg	Lutsey *et al.* 2014[86]
P	21–23 years	14 709 AA and Caucasian adults	45–64 years	34 % Increased HF risk in highest *v.* lowest quintile	Lutsey *et al.* 2014[86]
Ca	21–23 years	14 709 AA and Caucasian adults	45–64 years	24 % Increased HF risk in highest *v.* lowest quartile	Lutsey *et al.* 2014[86]
Vitamin C	Not reported	20 299 Healthy adults	39–79 years	38 % Decreased HF risk in highest *v.* lowest quartile of plasma vitamin C (P for trend <0·0001). 9 % decreased HF risk with each 20 µmol/l increase in plasma vitamin C concentration	Pfister *et al.* 2011[107]
Vitamin C	11 years	3919	60–79 years	19 and 25 % Decreased HF risk with each 1 SD increase in log-plasma vitamin C with and without previous MI. Significant decreases in relevant biomarkers (TAG, GGT, CRP, von Willebrand factor and NT-proBNP) and physiological parameters (HR, SBP) as well as risk of CHD across quartiles of plasma vitamin C	Wannamethee *et al.* 2013[104]
Vitamin E	11 years	3919	60–79 years	No association with HF	Wannamethee *et al.* 2013[104]
Vitamin E (α-tocopherol)	29 years	2321 (259 HF cases)	>50 years	No significant association	Ingelsson *et al.* 2005[106]
Fatty acids	Cross-sectional	86 Ambulatory patients with HF	53 years (mean)	TFA levels were positively associated with IL-1β ($P=0{\cdot}04$), IL-1 receptor antagonist ($P=0{\cdot}006$), IL-6 ($P=0{\cdot}006$), TNF ($P=0{\cdot}02$), TNF receptors 1 and 2 ($P=0{\cdot}03$ and 0·001), monocyte chemoattractant protein 1 ($P=0{\cdot}004$) and BNP ($P=0{\cdot}04$). However, TFA was positively associated with IL-10 ($P=0{\cdot}02$) and negatively associated with CRP ($P=0{\cdot}05$) and SAA ($P=0{\cdot}06$)	Mozaffarian *et al.* 2004[92]
Fatty acids	1 year	102 HF patients with ICD (NYHA II to III) and 25 controls	Not reported	Baseline omega-3 index was significantly lower ($P<0{\cdot}001$). 78 % decreased risk of ventricular arrhythmias in highest *v.* lowest omega-3 index ($P=0{\cdot}022$). In a multivariate analysis, the omega-3 index was the only independent predictor for ventricular arrhythmias up to 9 months	Wilhelm *et al.* 2008[153]
Fatty acids	14·3 years	3592 Adults	45–64 years	Higher SFA, especially myristic acid (14 : 0) and DGLA were associated positively with incident HF in both men and women. Higher arachidonic acid, Δ-5 desaturase index and long-chain *n*-3 PUFA, especially DHA, were associated inversely with HF in women, but not in men. 80 % decreased HF with highest *v.* lowest DHA quintile. 93 % increased HF risk in those in highest phospholipid palmitic acid quintile compared with lowest (P for trend $=0{\cdot}004$) after multivariate adjustment. 10 % increased HF risk in those in highest phospholipid palmitoleic acid quintile compared with lowest (P for trend $=0{\cdot}004$) after multivariate adjustment. No association with ALA, EPA, coA desaturase activity, phospholipid myristic acid, margaric acid, stearic acid or pentadecanoic acid and incident HF	Yamagishi *et al.* 2008[154]

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Table 5. *Continued*

Assessment(s)	Mean follow-up	Sample	Age	Outcome(s)	Reference
Fatty acids	Cross-sectional	308 Patients with dilative HF	48 years (mean)	*n*-3 DHA ($P<0·001$) and *n*-6 arachidonic acid (4·6 % ($P<0·01$)) were reduced whereas MUFA was increased ($P<0·01$) in patients with greater left ventricular dilatation	Rupp *et al.* 2010[81]
Fatty acids: long-chain *n*-3 fatty acids	15 years	2735 Adults	75 years (mean)	48 % Decreased HF risk in highest *v.* lowest quartile of plasma phospholipid EPA (P for trend = 0·001). Similar trends were observed for DPA and total long-chain *n*-3 ($P=0·057$, $P=0·062$) but not DHA ($P=0·38$)	Mozaffarian *et al.* 2011[77]
Fatty acids	Cross-sectional	183 Stable HF patients and 44 healthy controls	56 years (mean)	HF patients had decreased levels of several lipid parameters, several *n*-3 PUFA and higher plasma levels of NEFA, MUFA and palmitoleic acid compared with controls ($P<0·001$). These changes in fatty acid composition were significantly associated with functional class, impaired cardiac function (i.e. decreased cardiac index and increased plasma NT-proBNP) and enhanced systemic inflammation (i.e. increased hsCRP)	Øie *et al.* 2011[100]
Fatty acids	24 months	183 Stable HF patients and 44 healthy controls	56 years (mean)	Low levels of eicosatetraenoic acid and in particular high levels of vaccenic acid were significantly associated with total mortality. No association between NEFA and mortality. This study analysed non-fasting blood	Øie *et al.* 2011[100]
Fatty acids	> 22 years	788 Male, mostly Caucasian physicians with new-onset HF + 788 matched controls	58·7 years (mean)	Each 1 SD increase in plasma *cis*-palmitoleic acid was associated with 17 % increased HF risk. Each 1 SD increase of log-stearoyl-coA desaturase activity was associated with a 14 % increased HF risk	Djoussé *et al.* 2012[155]
Fatty acids	Not reported	109 HF patients with depression	Not reported	45 and 27 % Decreased risk of mortality per 0·1 units total *n*-3 and EPA	Jiang *et al.* 2012[156]
Fatty acids	Cross-sectional	85 Patients with stable HF	81 years (mean)	Decreased proportion of lauric acid and increased proportion of DGLA in HF + MetSyn *v.* HF without the MetSyn. DGLA showed positive correlations with BMI, waist circumference, and plasma TAG levels. Δ6 Desaturase was positively associated with plasma TAG, whereas Δ5 desaturase showed a negative correlation with plasma TAG and WC	Lee *et al.* 2012[157]
Fatty acids	14 years	2957 Adults	72 years (mean)	Plasma ALA was not associated with HF risk in multivariate analysis	Lemaitre *et al.* 2012[78]
Fatty acids	14 years	19 097 Adults	58·7 years (mean)	34 % Decreased HF risk in 4th *v.* lowest ALA quintile. However, the inverse relationship was non-linear (P quadratic trend = 0·02). 45 % decreased risk for HF in quintile 2 of plasma DPA. Plasma EPA and DHA were not associated with HF	Wilk *et al.* 2012[144]
Fatty acids	Subset analysis of RCT	852	64·4 years (mean)	Lower *n*-3 PUFA levels were independently associated with higher AF prevalence at study entry, but not with new occurrence	Aleksova *et al.* 2013[158]
Fatty acids	10·5 years	4248 Men and women	> 65 years	12 % Increased HF risk with each 1 SD higher plasma NEFA after multivariate analysis	Djoussé *et al.* 2013[159]
Fatty acids	2–4 years	712 Patients post-MI	57–73 years	68 and 69 % Increased HF mortality in those with low DHA or low EPA ($P=0·0358$ and $P=0·028$). 72 and 140 % increased HF hospitalisation with low DHA or low EPA ($P=0·0097$ and $P=0·1224$)	Hara *et al.* 2013[160]
Fatty acids	Not reported	7271 Adults: 3694 older adults from CHS and 3577 middle-aged adults from ARIC	Mean ages of 75·2 years (CHS) and 54·1 ± 5·8 years (ARIC)	34–57 % Increased HF risk in highest *v.* lowest quintile of erucic acid. 75–92 % increased HF risk in highest *v.* lowest quintile of nervonic acid	Imamura *et al.* 2013[72]
Fatty acids	Not reported	1203 HF patients	Not reported	EPA, but not DHA, was inversely related to CRP, pentraxin-3, adiponectin, natriuretic peptide and troponin levels	Masson *et al.* 2013[101]
Fatty acids	> 10 years	Mostly Caucasian physicians with new-onset HF + 788 matched controls	58·7 years (mean)	20 % Increased HF risk with each 1 SD higher plasma phospholipid palmitic acid ($P=0·042$) but not after Bonferroni correction ($P>0·008$). No associations between other SFA (14 : 0, 15 : 0, 18 : 0, 20 : 0 or 22 : 0) and HF risk (all P for trend >0·05)	Matsumoto *et al.* 2013[161]
Fatty acids	> 17·1 years	788 Male, mostly Caucasian physicians with new-onset HF + 788 matched controls	58·7 years (mean)	No relationship between *n*-6 PUFA and HF (P for linear trend = 0·39)	Petrone *et al.* 2013[162]

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Table 5. *Continued*

Assessment(s)	Mean follow-up	Sample	Age	Outcome(s)	Reference
Fatty acids	> 10 years	788 Male, mostly Caucasian physicians with new-onset HF + 788 matched controls	58·7 years (mean)	22 % Lower HF risk for each 1 SD of plasma *trans*-linoleic acid. Plasma *trans*-palmitoleic acid and oleic acid were not associated with HF risk ($P > 0{\cdot}0{\cdot}05$)	Tokede *et al.* 2013[163]
Fatty acids	15 years	421 HF cases and 421 matched controls	58 years (mean)	No significant associations between ALA or total long-chain *n*-3 fatty acids (EPA + DHA + DPA) and HF risk	Djoussé *et al.* 2014[79]
Fatty acids	> 10 years	788 Male, mostly Caucasian physicians with new-onset HF + 788 matched controls	58·7 years (mean)	Each 1 SD increase of *cis*-vaccenic acid was associated with a 41 % lower risk of HF with antecedent CHD (P for trend = 0·0004). Each 1 SD increase of log-stearoyl-coA desaturase activity was associated with 14 % increased HF risk. Oleic acid and *cis*-vaccenic acid concentrations were not related to HF risk. 67 % increased HF risk in highest *v.* lowest quintile of plasma phospholipid palmitoleic acids	Djoussé *et al.* 2014[164]
Fatty acids in EAT	Cross-sectional	30 Patients with systolic HF and 30 patients with normal systolic function	Not reported	Significantly higher levels of MUFA and palmitoleic acid in EAT of HF patients, whereas DHA levels were lower. EAT palmitoleic acid levels correlated with increasing left ventricular end-diastolic diameter and NT-proBNP	Fosshaug *et al.* 2015[165]
Fatty acids	560 d	685 Consecutive acute decompensated HF	76 years (mean)	Patients with adverse events had lower *n*-6 PUFA (arachidonic acid + DGLA) level than those without. *n*-3 PUFA (EPA + DHA) level was comparable between the groups. Lower *n*-6 PUFA was significantly associated with all-cause death and worsening HF, all-cause death, cardiovascular death and worsening HF ($P < 0{\cdot}001$, $P = 0{\cdot}005$, $P = 0{\cdot}021$, $P = 0{\cdot}019$, respectively). Lower *n*-6 PUFA was independently associated with increased risk of adverse events ($P = 0{\cdot}027$)	Nagai *et al.* 2016[166]
Fatty acids	Not reported	577 HF patients	Not reported	Cardiac mortality was significantly higher in the low EPA: arachidonic acid group than in the high EPA:arachidonic acid group (log-rank $P = 0{\cdot}004$). Multivariate Cox proportional hazard analysis revealed that the EPA: arachidonic acid ratio was an independent predictor of cardiac mortality ($P = 0{\cdot}041$)	Watanabe *et al.* 2016[167]

AA, African-American; ARIC, Atherosclerosis Risk in Communities Study; ALA, α-linolenic acid; BNP, B-type natriuretic peptide; CHS, Cardiovascular Health Study; CRP, C-reactive protein; DGLA, dihomo-γ-linolenic acid; DPA, docosapentaenoic acid; EAT, epicardial adipose tissue; GGT, γ-glutamyl transferase; HR, hazard ratio; hsCRP, high-sensitivity CRP; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; MetSyn, metabolic syndrome; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RCT, randomised controlled trial; SAA, *serum amyloid A;* SBP, systolic blood pressure; TFA, *trans*-fatty acid; WC, waist circumference.
* Except were specified, all studies were prospective cohort studies.

A low-Na, low-fat, largely plant-based diet is the basis for multiple CVD dietary regimens. The Rice Diet has never been subjected to a randomised controlled trial but it is interesting to note that results of the Rice Diet seem to have first been published in 1946, predating other CVD dietary regimens by about 50 years.

Low-fat, plant-based diet. Low-fat diets have been and remain the cornerstone of cardiovascular dietary advice. A low-fat, plant-based diet, as part of an overall healthful lifestyle programme, remains the only dietary pattern to be objectively proven to reverse CHD[40–42]. To date, a low-fat, plant-based diet has not been subjected to a trial specific to HF incidence or outcome. Nevertheless, the remarkable effect sizes reported in these trials is worthy of further investigation in CVD, including HF.

The PREDIMED trial used a low-fat diet in the control group. Both intervention diets (i.e. MedDiet + EVOO or nuts) displayed significant decreases in multiple non-HF, CVD endpoints. However, the authors acknowledge that 'changes in total fat were small' in the low-fat group. Because the participants in the 'low-fat' diet group did not follow a low-fat diet, this trial cannot conclude a superiority of the MedDiet over a low-fat diet.

A recent case report demonstrated the effects of a plant-based diet in a 79-year-old male with documented triple vessel disease (80–95 % stenosis) and left ventricular systolic dysfunction (ejection fraction = 35 %) in the context of progressive dyspnoea. In the study, 2 months of a low-fat, plant-based diet led to clinically significant reductions in body weight and lipids with improved exercise tolerance and ejection fraction (+15 %)[43].

Further, several relevant clinical trials are detailed in Table 6[44–47].

A 2005 review suggested that certain lifestyle measures, including plant-based diets (moderate to low in bioavailable

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Table 6. Intervention trials of diet and heart failure (HF) risk and/outcome

Intervention	Design	Control?	Duration	Sample	Age	Outcome(s)	Reference
Dietary patterns							
Energy restriction ± exercise	Four-arm RCT	Attention control	20 weeks	100 Older, obese subjects with HFpEF	67 years (mean)	Energy restriction and exercise intervention significantly increased peak O_2 consumption (+1·3 *v.* +1·2 ml/kg body mass per min, respectively). Combined energy restriction + exercise was superior for peak O_2 consumption and weight loss	Kitzman *et al.* 2016[168]
DASH	Two-arm RCT	Control	Three consecutive 30 d intervention feeding periods	375 Adults with high-normal BP	48 years (mean)	Steepening of slope between BP and natriuresis ($P = 0·0002$), suggesting a natriuretic effect	Akita *et al.* 2003[22]
DASH-DHF	Non-blinded, non-randomised and non-controlled	No	3 weeks	13 Clinically stable, primarily obese postmenopausal women with HFpEF and multiple co-morbidities	72 years (mean)	Decreases in 24 h BP, dyspnoea, urinary Na, BNP and oxidative stress but an increase in 24h urinary K and aldosterone. Trend towards increased exercise capacity (6MWT) ($P = 0·06$)	Hummel *et al.* 2012[23]
DASH-DHF	Non-blinded, non-randomised and non-controlled	No	3 weeks	13 Clinically stable, primarily obese postmenopausal women with HFpEF and multiple co-morbidities	72 ± 10 years	Significant increases in SV ($P = 0·02$), EF ($P = 0·03$) and contractility ($P = 0·01$) but a significant decrease in arterial elastance ($P = 0·07$), viscoelastic/relaxation ($P = 0·03$) and chamber stiffness ($P = 0·03$)	Hummel *et al.* 2013[24]
DASH-DHF	Non-blinded, non-randomised and non-controlled	No	3 weeks	13 Clinically stable, primarily obese postmenopausal women with HFpEF and multiple co-morbidities	72 ± 10 years	Increases in short-chain acyl carnitines which correlated with improved LVF, suggesting improved myocardial energy utilisation	Mathew *et al.* 2015[25]
DASH	Non-blinded RCT	General HF dietary recommendations	12 weeks	48 HF patients (NYHA classes I–III)	62 years (mean)	Large artery elasticity improved significantly after 4 weeks ($P < 0·01$) but less pronounced at 8 and 12 weeks. Significant improvement in 6MWT ($P = 0·018$) and QoL ($P = 0·006$). BNP decreased ($P = 0·081$)	Rifai *et al.* 2015[26]
MedDiet	Randomised single-blind trial	Usual care	27 months	605 MI survivors	53·5 years	76 % Reduction in composite end point (including HF) survival ($P < 0·0001$). 75 % reduction in HF specifically	De Lorgeril *et al.* 1996[30]
MedDiet	Randomised single-blind trial	Usual care	46 months	605 MI survivors	53·5 years	69·6 % Reduction in composite end point (including HF) survival ($P = 0·0001$). 45 % reduction in HF specifically	De Lorgeril *et al.* 1999[31]
MedDiet (*n* 51) or low-fat diet (*n* 50)	Three-arm RCT	Usual care (*n* 101)	46 months	202 Subjects after a first MI	Not reported	Both diet groups had superior survival (84 %) compared with usual care (60 %) ($P < 0·001$) with no superiority between diets	Tuttle *et al.* 2008[34]
MedDiet + extra-virgin olive oil or nuts *v.* low-fat diet	Three-arm RCT	Low–moderate-fat diet	1 year	930 Adults at high CVD risk	Not reported	Both MedDiets decreased plasma NT-proBNP *v.* control group ($P < 0·05$) and oxidised LDL decreased in both groups ($P < 0·05$), lipoprotein(a) increased in control group but not in either MedDiet group ($P = 0·046$)	Fitó *et al.* 2014[35]
MedDiet + virgin olive oil or nuts *v.* low-fat diet	Three-arm RCT	Low–moderate-fat diet	4·8 years	7403 Adults at high CVD risk	Not reported	No effect on HF incidence – possibly due to underpowering	Papadaki *et al.* 2017[32]

Table 6. *Continued*

Intervention	Design	Control?	Duration	Sample	Age	Outcome(s)	Reference
High-protein hypoenergetic diet	Three-arm RCT	Standard-protein hypoenergetic diet or normoenergetic AHA recommendations	12 weeks	14 Overweight/obese subjects with HF + DM (NYHA classes II–III)	Not reported	Significantly greater reductions in weight ($P = 0{\cdot}005$), percentage body fat ($P = 0{\cdot}036$), TC ($P = 0{\cdot}016$), TAG ($P = 0{\cdot}034$) and LDL ($P = 0{\cdot}041$) as well as greater improvements in exercise capacity (6MWT) ($P = 0{\cdot}01$) and VO_2 peak ($P = 0{\cdot}003$), HDL ($P = 0{\cdot}006$) and QoL scores ($P = 0{\cdot}022$). A trend towards increased muscle mass in the high-protein group	Evangelista *et al.* 2009[51]
Nordic Nutrition Recommendation diet (*ad libitum*)	RCT	'Paleo' diet (*ad libitum*)	24 months	68 Overweight postmenopausal women	Not reported	Non-significant decreases in weight but significant decrease in LVM ($P < 0{\cdot}05$ for both diets) and end diastolic volume ($P < 0{\cdot}05$ for both diets). SV and CO decreased over time with no difference between groups	Andersson *et al.* 2016[52]
Low-fat plant-based diet + exercise, stress management	RCT	Usual care	24 d	46 CHD patients	Not reported	Significant increases in exercise capacity and LVEF with decreases in TC and frequency of anginal episodes	Ornish *et al.* 1983[40]
Low-fat plant-based diet (more fruit, vegetables, nuts and grain products)	Single-blind RCT	Diet B (low fat alone)	1 year	406 Patients with acute MI and unstable angina	50·5 years (mean)	Decreases in body weight of 6·3 kg (group A) and 2·4 kg (group B). Compared with those in group B, subjects in group A had significant reductions in TC, LDL, TAG and fasting BG (all $P < 0{\cdot}01$) and BP ($P < 0{\cdot}05$) but a significant increase in HDL ($P < 0{\cdot}05$). Group A experienced significant reductions in CVE, including HF incidence ($P < 0{\cdot}001$) and total mortality ($P < 0{\cdot}01$)	Singh *et al.* 1992[44]
Low-fat plant-based diet + exercise, stress management	Non-randomised, non-blinded	No	1 year	50 Patients with LVEF ≤40 % and 186 patients with LVEF >40 %	56·2 years (mean)	Regardless of baseline LVEF, there were significant improvements in lifestyle behaviours, body weight, body fat, BP, RHR, TC and LDL-cholesterol, exercise capacity, and QoL by 3 months ($P < 0{\cdot}05$ for all). Improvements in body weight, diastolic BP, TC and LDL were maintained over 1 year	Pischke *et al.* 2007[45]
Low-fat plant-based diet + exercise, stress management	Non-randomised, non-blinded	Usual care + revascularisation	3 years	27 CHD patients with asymptomatic reduced LVEF	Not reported	Control group experienced 1227 % increased CVE at 3 months and 175 % at 3 years. Of those in the lifestyle change group, 88 % did not require primary revascularisation	Pischke *et al.* 2010[46]
Low-fat plant-based diet	Non-randomised, non-blinded	No	2 months	One male (case study) with triple vessel disease (80–95 % stenosis), LVSD (EF 35 % and progressive dyspnoea)	79 years	Clinically significant reductions in body weight and lipids with improved exercise tolerance and EF (+15 %)	Choi *et al.* 2017[43]
Dietary components							
Cocoa – one bar commercially available flavanol-rich chocolate	DBRCT	Cocoa liquor-free control chocolate	2 h	20 CHF patients	59·2 years (mean)	FMD improved from 4·98 to 5·98 ($P = 0{\cdot}045$) while platelet adhesion significantly decreased from 3·9 to 3·0 % ($P = 0{\cdot}03$). No effect on endothelial-independent vasodilatation, BP or heart rate	Flammer *et al.* 2012[169]
	DBRCT		4 weeks	20 CHF patients			

Table 6. *Continued*

Intervention	Design	Control?	Duration	Sample	Age	Outcome(s)	Reference
Cocoa – two bars commercially available flavanol-rich chocolate/d		Cocoa liquor-free control chocolate			59·2 years (mean)	FMD improved from 4·98 to 6·86 % ($P=0·03$). No effect on endothelial-independent vasodilatation, platelet adhesion, BP or heart rate	Flammer *et al.* 2012[169]
Cocoa – four small chocolate squares and cocoa beverages daily (100 mg (–)-epicatechin)	Open-label pilot study	No	3 months	Five HF patients (NYHA stages II–III) with T2DM	47–71 years (mean)	Significant increase in HDL ($P=0·05$) and trend to decreased BNP ($P=0·06$)	Taub *et al.* 2012[170]
Cocoa – 100 mg (–)-epicatechin (Epi)-rich cocoa	Unblinded, uncontrolled, case–control pilot study	No	3 months	Five T2DM/HF (NYHA stages II–III) patients and three age- and sex-matched healthy controls	60·8 years (mean)	Intervention normalised skeletal muscle glutathione and total carbonylation/nitrotyrosilation levels in cases and significantly increased SIRT3 protein levels and SOD2. Significant increase in HDL and trend to decreased BNP ($P=0·06$)	Ramirez-Sanchez *et al.* 2013[171]
Cocoa – four small chocolate squares and cocoa beverages daily (100 mg (–)-epicatechin)	Open-label pilot study	No	3 months	Five HF patients (NYHA stages II–III) with T2DM	47–71 years	Intervention induced recovery/enhancement of DAPC protein levels, sarcomeric microstructure and markers of skeletal muscle growth/differentiation consistent with myofibre regeneration. VO_2max increased by 24 % (NS)	Taub *et al.* 2013[172]
Cocoa – 50 g/d of high-flavanol dark chocolate (1064 mg flavanols/d)	Randomised, cross-over	Low-flavanol dark chocolate (88 mg flavanols/d)	4 weeks	24 CHF patients, stable on guideline-directed medical therapy	70 years (mean)	Greater decrease in NT-proBNP and DBP after high-flavanol dark chocolate compared with low-flavanol dark chocolate ($P=0·019$ and $<0·001$)	De Palma *et al.* 2016[173]
Dietary inorganic nitrate (11·2 mmol)	DBRCT cross-over	Matched, nitrate-depleted beetroot juice	2 h	9 Non-ischaemic cardiomyopathy patients	57 years (mean)	Increased breath NO ($P<0·05$) as well as increased peak knee extensor power ($P<0·05$), maximal power ($P<0·05$) and maximal velocity of knee extension ($P<0·05$)	Coggan *et al.* 2015[109]
Dietary inorganic nitrate (12·9 mmol)	DBRCT cross-over	Matched, nitrate-depleted beetroot juice	3 h	17 HFpEF patients	65·5 years (mean)	Increased plasma NOx metabolites ($P=0·0003$), peak VO_2 ($P=0·005$) and total work performed ($P=0·04$) and CO ($P=0·006$) but significant decreases in systemic vascular resistance ($P=0·03$) and aortic augmentation index ($P=0·03$)	Zamani *et al.* 2015[110]
Dietary inorganic nitrate (6·1 mmol/d)	DBRCT cross-over	Matched, nitrate-depleted beetroot juice	1·5–2 h	20 HFpEF patients	69 years (mean)	Significantly reduced resting BP ($P<0·001$) and increased plasma NOx ($P<0·001$) but no ergonomic effect	Eggebeen *et al.* 2016[111]
Dietary inorganic nitrate (6·1 mmol/d)	Unblinded, uncontrolled trial	No	7 d	20 HFpEF patients	69 years (mean)	Significantly reduced resting BP ($P<0·001$) and increased plasma NOx ($P<0·001$) as well as submaximal aerobic endurance ($P=0·02$)	Eggebeen *et al.* 2016[111]
Dietary inorganic nitrate (12·9 mmol/d)	DBRCT cross-over	Matched, nitrate-depleted beetroot juice	3 h	11 Non-ischaemic, dilated cardiomyopathy patients	56 years (mean)	Significant increases in plasma NOx ($P<0·005$) and exercise capacity ($P=0·0056$)	Kerley *et al.* 2016[112]
Dietary inorganic nitrate (12·9 mmol/d)	DBRCT cross-over	Matched, nitrate-depleted beetroot juice	9 d	10 HFrEF patients (LVEF ≤40 %)	63 years (mean)	Significant increase in plasma nitrite ($P<0·05$). No difference in time to exercise intolerance or central haemodynamics, arterial BP, pulmonary O_2 uptake kinetics, skeletal muscle oxygenation, or blood lactate concentration	Hirai *et al.* 2017[174]

Table 6. *Continued*

Intervention	Design	Control?	Duration	Sample	Age	Outcome(s)	Reference
n-3 PUFA (1 g/d), vitamin E (300 mg/d) or both	2 × 2 factorial, DBRCT	Placebo	3·5 years	11 324 Patients surviving recent MI	Not reported	10 % Decreased risk of death, non-fatal MI/ stroke with *n*-3 PUFA. Supplemental vitamin E had no effect	Anonymous, 1999[175]
n-3 PUFA (8 g/d)	DBRCT	Placebo	18 weeks	14 HF patients (NYHA stages III–IV)	Not reported	TNF-α and IL-1 decreased with *n*-3 PUFA ($P = 0{\cdot}02$ and 0·09). TNF-α increased with placebo ($P = 0{\cdot}07$)	Mehra *et al.* 2006[95]
n-3 PUFA (1·8 g EPA and 1·2 g DHA)	DBRCT cross-over	Placebo (olive oil)	6 weeks	20 HF patients (NYHA stages II–III)	> 65 years	FBF was greater after *n*-3 PUFA compared with baseline and placebo ($P < 0{\cdot}05$)	Morgan *et al.* 2006[176]
n-3 PUFA (2 g/d)	DBRCT	Placebo	4 months	25 Patients with post-MI LVD (EF <40 %)	Not reported	With *n*-3 PUFA, there were increases in reflex depressor ($P < 0{\cdot}01$) and bradycardiac responses ($P < 0{\cdot}04$), spontaneous baroreflex sensitivity ($P < 0{\cdot}02$), R-R interval total variance and spectral powers (both low-frequency and high-frequency)	Radaelli *et al.* 2006[177]
n-3 PUFA (1 g/d)	DBRCT	Placebo	3·9 years	6975 Subjects with HF (NYHA stages II–IV)	Not reported	With *n*-3 PUFA there was a 7 % decrease in all-cause mortality ($P = 0{\cdot}041$) and a 3 % decrease in combined mortality and cardiovascular admission ($P = 0{\cdot}009$)	Tavazzi *et al.* 2008[70]
n-3 PUFA (1 g/d) (R1)	2 DBRCT	Rosuvastatin 10 mg daily	Not reported	6975 and 4574 HF patients	Not reported	*n*-3 PUFA, but not rosuvastatin, significantly decreased risk of death and cardiovascular admission	Marchioli *et al.* 2009[178]
n-3 PUFA (2 g/d)	DBRCT	Placebo	3 months	77 Elderly patients with HF	Not reported	Significant decreases in plasma TNF-α, IL-6, intercellular adhesion molecule 1 and NT-proBNP. Small, non-significant improvement in LVEF	Zhao *et al.* 2009[96]
n-3 PUFA (0·9 g/d)	DBRCT	Olive oil	24 weeks	38 HF patients with NYHA classes II–III HF	Not reported	Significant reduction was observed in P-selectin	Eschen *et al.* 2010[179]
n-3 PUFA + rosuvastatin; *n*-3 PUFA + placebo; placebo + rosuvastatin; placebo + placebo	2 × 2 factorial DBRCT	Placebo	3 years	608 HF patients	66 years (mean)	LVEF increased with *n*-3 PUFA and placebo but to a greater extent with *n*-3 PUFA at 1, 2 and 3 years ($P = 0{\cdot}005$). No other echocardiographic parameter changed significantly	Ghio *et al.* 2010[180]
n-3 PUFA (1 g/d)	DBRCT	Placebo	2·5 years	566 HF who received an ICD	Not reported	Non-significant decrease in time to first appropriate ICD discharge ($P = 0{\cdot}152$). Those with highest 3-month increase in plasma *n*-3 PUFA had lower incidence of arrhythmic events	Finzi *et al.* 2011[181]
n-3 PUFA (1 or 4 g/d)	DBRCT	Placebo	3 months	43 Patients with severe, non-ischaemic HF	Not reported	LVEF increased in a dose-dependent manner ($P = 0{\cdot}01$ for linear trend) in both *n*-3 PUFA groups, whereas FMD ($P = 0{\cdot}01$) and maximal exercise effort increased while IL-6 decreased ($P = 0{\cdot}03$) only with 4 g *n*-3 PUFA	Moertl *et al.* 2011[98]
n-3 PUFA (1 or 4 g/d)	DBRCT	Placebo	3 months	36 Patients with severe, non-ischaemic HF (LVEF <35 %, NYHA class >2)	Not reported	Monocyte–platelet aggregates and plasma TF decreased in a dose-dependent manner ($P = 0{\cdot}02$ for both linear trends), whereas P-selectin, high-sensitivity IL-6 and prothrombin fragment F1·2 decreased only with 4 g *n*-3 PUFA ($P = 0{\cdot}03$, $P < 0{\cdot}01$ and $P = 0{\cdot}03$)	Moertl *et al.* 2011[99]

Table 6. *Continued*

Intervention	Design	Control?	Duration	Sample	Age	Outcome(s)	Reference
n-3 PUFA (2 g/d)	DBRCT	Placebo	12 months	133 Non-ischaemic dilated cardiomyopathy	64 years (mean)	LVEF, peak VO_2, exercise capacity increased ($P<0·001$) while NYHA and HF hospitalisation rates decreased ($P<0·001$ and $P=0·0002$)	Nodari *et al.* 2011[182]
n-3 PUFA (2 g/d)	DBRCT	Placebo	6 months	70 Patients with HF who had a tri-chamber pacemaker and automated defibrillator	57 years (mean)	BNP and late diastolic velocity index decreased ($P<0·005$ and $P=0·04$), while myocardial performance index increased ($P=0·011$). No effect on mortality and hospitalisation	Kojuri *et al.* 2013[183]
n-3 PUFA (1 g/d)	DBRCT	Placebo	12 months	388 HF patients	Not reported	An increase in mean R-R interval, standard deviation of all normal-to-normal R-R intervals, very low-frequency power (all $P<0·05$) and turbulence slope ($P=0·05$). No longer significant at 12 months	La Rovere *et al.* 2013[184]
n-3 PUFA (1 g/d)	DBRCT	Placebo	3 months	1203 HF patients	Not reported	Increased plasma EPA and DHA but decreased pentraxin-3	Masson *et al.* 2013[101]
n-3 PUFA (as EPA)	No randomised trial	No *n*-3 PUFA	12 months	139 HF patients	Not reported	LVEF increased but MCP-1 and ADMA decreased both $P<0·001$). Only those with dyslipidaemia were treated with EPA. EPA treatment was an independent predictor of CVE ($P=0·031$)	Kohashi *et al.* 2014[185]
n-3 PUFA (6·5 g/d) and L-alanyl-L-glutamine (8 g/d)	DBRCT	Placebo (safflower-seed oil and milk powder)	3 months	31 HF patients	59 years (mean)	Increases in lean body mass and QoL (both $P=0·04$). Non-significant decrease in TAG and increase in peak VO_2. No differences in muscle function, ECG, 6MWT or hand-grip strength. No differences in muscle fibre composition, fibre cross-sectional area, gene expression of metabolic marker genes and skeletal muscle oxidative capacity	Wu *et al.* 2015[186]
n-3 PUFA (1 g/d)	RCT	Placebo	6 months	205 HF patients	Not reported	Significant decreases in BNP, end-diastolic left ventricle dimension and end-systolic left ventricle dimension, maximum diameter of left atrium and TDI Etv/Atv ($P=0·001$, 0·047, 0·01, 0·004 and 0·038). Left atrium EF increased ($P=0·021$)	Chrysohoou *et al.* 2016[187]
Probiotic *Saccharomyces boulardii* (1000 mg/d)	DBRCT	Placebo	12 weeks	20 HF patients	Not reported	Significant decreases in TC ($P=0·01$), uric acid levels ($P=0·014$), left atrial diameter ($P=0·044$), hsCRP ($P=0·011$) and improvement in LVEF ($P=0·005$)	Costanza *et al.* 2015[103]
Vegetable juice (29·4 mg lycopene)	RCT	Usual care	30 d	40 HF patients	65 years	Increased plasma lycopene ($P=0·02$) and decreased CRP in women only ($P=0·04$)	Biddle *et al.* 2015[102]

6MWT, 6-minute walk test; ADMA, asymmetric dimethylarginine; AHA, American Heart Association; Atv, peak late diastolic tissue velocity; BG, blood glucose; BNP, B-type natriuretic peptide; BP, blood pressure; CO, cardiac output; CHF, congestive HF; CRP, C-reactive protein; CVE, cardiovascular events; DAPC, dystrophin-associated protein complex; DASH, Dietary Approaches to Stop Hypertension; DASH-DHF, Dietary Approaches to Stop Hypertension in Diastolic Heart Failure (50 mmol or 1150 mg Na per 2100 kcal (8786 kJ)); DBRCT, double-blind, randomised controlled trial; DM, diabetes mellitus; ECG, electrocardiogram; EF, ejection fraction; Etv, peak early diastolic tissue velocity; FBF, forearm blood flow; FMD, flow-mediated dilation; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hsCRP, high-sensitivity C-reactive protein; ICD, *implantable cardioverter-defibrillator*; LVD, left ventricular dysfunction; LVEF, left ventricular ejection fraction; LVF, left ventricular function; LVM, left ventricular mass; MCP-1, monocyte chemoattractant protein-1; MedDiet, Mediterranean diet; MI, myocardial infarction; NOx, NO metabolites; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; QoL, quality of life; R-R interval, cycle length variability; RCT, randomised controlled trial; RHR, resting heart rate; SIRT-3, sirtuin-3; SOD2, superoxide dismutase-2; SV, stroke volume; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TDI, tissue Doppler imaging.

phosphate), might modulate parathyroid hormone secretion and reduce left ventricular hypertrophy as well as HF risk[48]. Similarly, a 2014 editorial regarding a prospective study of processed/unprocessed red meat consumption and HF risk[49] suggested that plant-rich diets could lower HF incidence and severity[50]. Taken together, these reports suggest that not only are comprehensive lifestyle changes potentially effective but are also achievable and sustainable, even for those with severe disease.

High-protein diets. Two small trials have demonstrated benefit of high-protein diets in HF, perhaps due to energy restriction[51,52] (Table 6). Interestingly, patients in the high-protein group were encouraged to increase plant sources of protein as opposed to animal sources. This pilot study did not report actual dietary intake but it is likely that consumption of nuts, seeds, legumes and soya products increased[51].

Conversely, excess dietary protein may be harmful to HF. One pilot study reported a decrease in stroke volume and cardiac output with either high-protein Nordic recommendations or the Paleolithic diet[52]. Further, protein-bound uraemic toxins (PBUT) are derived from the colonic microbiota metabolism of dietary amino acids. Evidence linking PBUT to adverse CVD outcomes has been accumulating. Recent reviews on PBUT suggest that a low-protein diet may reduce PBUT with beneficial effects on CVD[53,54]. However, there is a lack of interventional evidence. Nevertheless, some dietary patterns discussed above could be considered low–moderate protein. More research in this area is warranted regarding high-protein diets but caution is warranted regarding HF patients with advanced disease and co-morbidities (for example, renal disease).

Studies based on overall diet quality. One spurious cross-sectional study among subjects with advanced HF unexpectedly reported that dietary habits typically considered healthy (reduced intake of foods high in saturated fats and frequent consumption of fruits and vegetables) were related to impaired quality of life[55]. However, this study contrasts with other evidence (Tables 2–6) and as such may represent reverse causation whereby a HF diagnosis may lead to healthier dietary habits as opposed to improved diet causing severe HF.

There are several other spurious reports of dietary pattern and HF incidence/outcome. The Alternate Healthy Eating Index (AHEI), a nine-component index, was designed to assess food choices and macronutrient sources associated with reduced chronic disease risk[56]. The nine components include vegetables, fruit, nuts and soya protein, cereal fibre, multivitamin use, low in *trans*-fat and alcohol, as well as high PUFA:SFA and white meat:red meat ratios. A healthy lifestyle, including a high AHEI score, was associated with a 77 % reduction in HF incidence[13]. Further, two prospective studies demonstrated that a higher AHEI score was associated with reduced HF incidence (Table 4). One of these studies was a prospective analysis of two combined trials of anti-hypertensive medication[57]. A protective effect of higher AHEI score was observed regardless of receipt of proven medications or presence of co-morbidities/risk factors, suggesting that diet can be protective in the absence of pharmacology but can also act synergistically[57]. An additive benefit of nutrition to pharmacology was reported in one the first reports of the MedDiet and CVD[31].

Several reports have associated higher overall diet quality with decreased HF incidence, including the Dietary Modification Index, Diet Risk Score and Dietary Inflammatory Index.

The Diet Risk Score is based on food items that are considered predictive (meat, salty snacks and fried foods) or protective (fruits and green leafy vegetables, other cooked vegetables and other raw vegetables) of CVD/HF[57]. The Dietary Modification Index score is based on percentage of total energy intake from fat, vegetables and fruit servings, grain servings, percentage of energy intake from saturated fat, percentage of energy intake from *trans*-fat and dietary cholesterol intake[58]. The Dietary Inflammatory Index was developed to characterise dietary intake from maximally anti- to pro-inflammatory[59]. Scores on these diet quality scales have been inversely associated with HF incidence (Tables 3–6).

Evidence linking dietary components with heart failure

As mentioned above, the effect of a single food or nutrient may be confounded by dietary habits and patterns[19]. However, studies of single foods/nutrients can provide additional information. Further, nutritional research has traditionally focused on single foods/nutrients. Evidence for specific foods and dietary components regarding HF incidence/severity is detailed in Tables 2–6.

Briefly, fruit, vegetable, whole grain and chocolate consumption was inversely associated with HF incidence/severity, while processed and/or red meat and dairy were positively associated. Although two early prospective studies reported a positive association between egg consumption and HF incidence[60,61], a subsequent prospective study reported no association in women or diabetics and a positive association in men, but only with >6 eggs weekly[62]. Nevertheless, a 2017 meta-analysis reported an elevated risk of incident HF associated with frequent egg consumption[63].

Interestingly, any protective effect of fish may be influenced by its preparation (fried *v.* non-fried) and type (i.e. oily *v.* non-oily)[64]. Increased consumption of baked or broiled fish has been inversely associated with HF risk, whereas higher consumption of fried fish was associated with a higher risk of incident HF. Further, fried fish has been associated with reduced ejection fraction, lower cardiac output and higher systemic vascular resistance in older adults[64]. There are three meta-analyses of fish intake and HF risk. Two meta-analysis reported an inverse association between HF risk and oily fish consumption[65,66]. However, a third meta-analysis reported no significant association, except for a positive association with fried fish[67]. The seemingly inconsistent observations may be partially related to toxins (for example, Hg). Alternatively, it is possible that dietary displacement may explain the inconsistencies. For example, if consumed in place of red/processed meat or eggs, fish may appear protective; however, if consumed in place of vegetables or whole grains, fish may not be protective. There are no randomised trials of fish consumption in HF.

One potentially important aspect of fish is *n*-3 fatty acids. Several small trials of *n*-3 supplementation in HF are detailed in

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Table 6. A recent meta-analysis of randomised controlled trials supported selected benefit of *n*-3 in HF[68]. A 2017 science advisory from the American Heart Association regarding *n*-3, based mostly on secondary prevention trials in those at high risk of CVD, suggested that those with recent myocardial infarction or current HF may benefit from supplementation[69]. This HF recommendation is based on a single, large randomised, double-blind, placebo-controlled trial examining the effect of *n*-3 supplementation in patients with chronic HF[70]. Interestingly, in an earlier trial, dietary intervention was superior to usual care but a low-fat diet was as effective as the MedDiet, despite containing less *n*-3[34], suggesting that *n*-3 intake may not be as beneficial in the context of a low-fat, plant-based diet.

Several findings from large, observational studies of nutrition and HF deserve discussion. In one prospective one study, processed red meat was associated with HF incidence and mortality, while unprocessed red meat was not[49]. This null finding regarding unprocessed red meat should be interpreted with caution because the difference between the groups with the highest and lowest consumption was <1 serving/d. An accompanying editorial suggested 'one possibility is that high intakes of red and other meat might displace micronutrient-rich plant foods from the diet and thus lead to micronutrient deficiencies that promote HF' and concluded by stating 'there is an urgent need to educate patients and the general public about the adverse health effects of red and processed red meat consumption'[50].

A recent dose–response meta-analysis of >1 million participants reported no association between increasing dietary Mg intake and total CVD risk. However, there was a significant 31 % reduction in HF risk[71]. Rich dietary sources of Mg include vegetables, legumes and nuts.

Evidence from specific studies of dietary patterns linking dietary components with heart failure

Several studies of dietary patterns discussed above also assessed the effects of individual foods and/or food components.

Multivariate analysis of the Women's Health Initiative Observational Study suggested a protective association of a diet low in cholesterol ($P=0{\cdot}001$) and high in fibre ($P=0{\cdot}026$) regarding HF[58].

A prospective analysis of the AHEI and HF incidence from two combined pharmacology trials was introduced above[57]. The authors further analysed each component of the AHEI, noting that all types of vegetables, green leafy vegetables, other raw vegetables, fruit, soya protein and nuts were inversely associated with HF incidence, while meat, poultry and eggs were positively associated with increased risk. There was no association with fish[57].

A 2013 analysis of two prospective cohort studies demonstrated a positive association between plasma long-chain MUFA and HF incidence. Multiple foods related to plasma long-chain MUFA include fish, salad oils, poultry, processed meats, mustard seeds/oil and mixed meals (for example, pizza, meat sandwiches)[72].

In one prospective study, a greater MedDiet score was associated with decreased risk of CVD incidence/recurrence. Of the overall dietary pattern, only consumption of vegetables, salads and nuts was associated with lower risk of recurrent cardiac events (including HF)[73]. A cross-sectional study by the same group reported that fish, olive oil, pasta and moderate alcohol were associated with improved echocardiography parameters[74]. In contrast, the MedDiet was not associated with HF risk in multivariate analysis in a separate prospective study[75]. However, when dairy products were excluded, a significant protective association was observed. Further, only moderate alcohol (moderate *v.* low/high intakes) and fish were significantly associated with decreased HF incidence, while meat was the only factor significantly positively associated with HF incidence[75].

A prospective study of Mediterranean and DASH diet scores on mortality in women with HF was discussed above. Interestingly, the specific diet score components inversely associated with HF mortality were vegetables, nuts and whole grains[36]. This is consistent with a 2009 prospective study in which moderate consumption of alcohol, low consumption of meat/meat products, and high consumption of vegetables, fruits, nuts, olive oil and legumes were the MedDiet components inversely associated with all-cause mortality[29].

Biomarker studies. Nutritional studies generally suffer from a lack of objective measure of dietary intake. Several nutrients can be measured in serum or plasma. Multiple studies have assessed blood nutrient levels and HF incidence/severity (Table 4). The Lyon Diet Heart study was briefly introduced above (MedDiet section). This secondary prevention trial noted striking decreases in CVD, including HF, in conjunction with increased plasma vitamins C and E as well as increased plasma *n*-3 and decreased *n*-6 fatty acids (linoleic and arachidonic acids)[30]. Multiple additional studies demonstrate an inverse association between blood antioxidant level (β-carotene, lycopene, vitamin C) and HF incidence/severity, although this is not fully consistent[76]. Further, there is evidence that plasma micronutrient level is lower in more severe HF but also that ejection fraction correlates with multiple micronutrients. Similarly, serum/plasma *trans*-fatty acids and SFA were positively associated with HF incidence/severity, while long-chain PUFA were negatively associated.

Most of these studies relied on a single measurement; however, levels can change over time. Nevertheless, several studies reported modest correlations (r 0·2–0·6) between plasma fatty acids measured in samples from studies of HF incidence collected 6–15 years apart[77–79], suggesting that measurement of fatty acids at a single time point may be sufficient. In fact, the proportion of long-chain *n*-3 fatty acids in erythrocytes has been proposed as a HF risk factor[80,81].

Although it is attractive to assume that serum and plasma reflect dietary intake alone, additional factors may be present in HF such as increased requirements, impaired intestinal absorption, alteration in renal reabsorption, impaired cellular regulation and increased losses secondary to increased oxidant stress and/or medications, for example, diuretics[82]. One study demonstrated decreased plasma vitamin C in HF patients compared with controls despite similar intake[83]. Regardless of

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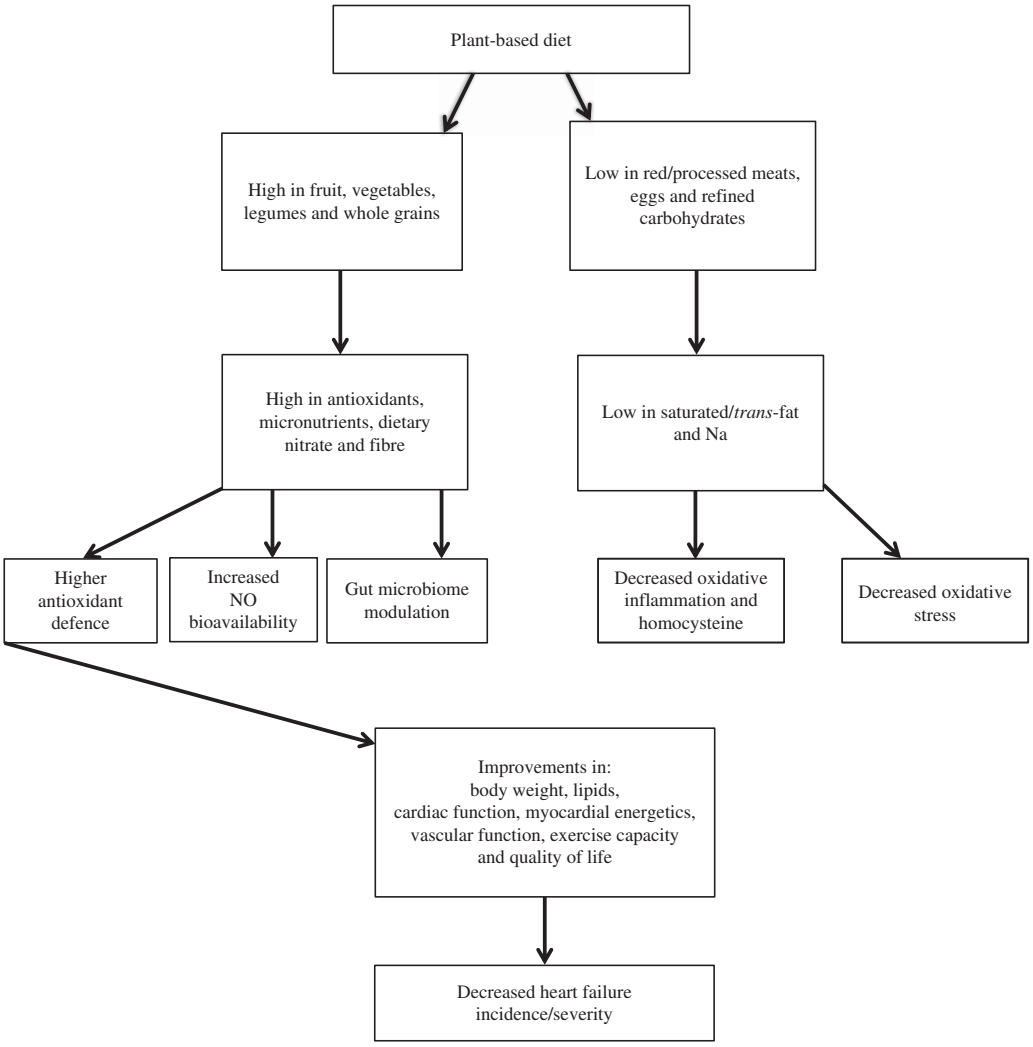

Fig. 1. Cardioprotective effects of a plant-based diet.

the cause(s) of altered blood nutrients in HF, it is likely that dietary modification regarding these nutrients will prove beneficial to preventing/treating HF.

Potential mechanisms

Although existing research is limited, dietary patterns associated with decreased HF incidence/severity have several common features, i.e. high in micronutrients, antioxidants, nitrate and fibre but low in animal protein/fat as well as saturated/*trans*-fatty acids, Na and bioavailable phosphate[49,50,60,75,84–87]. It is likely that these features contribute to decreased oxidative stress[88–91] and inflammation[47,92–104] but higher antioxidant defence[83,88–91,104–108] and NO bioavailability[109–112] (see Fig. 1).

Another potential mechanism is dietary modulation of the gut microbiome. A series of well-conducted human studies demonstrated that the intestinal microbiota metabolise choline/phosphatidylcholine and L-carnitine to produce trimethylamine, which is oxidised to proatherogenic trimethylamine *N*-oxide (TMAO)[113,114]. TMAO levels are elevated in HF compared with controls[115]. Further, TMAO levels have been correlated with brain-type natriuretic peptide[116] and associated with HF severity[115–118] and HF mortality[115,116,118]. Foods rich in L-carnitine (for example, red meat) and choline/phosphatidylcholine (for example, eggs) have been linked with HF incidence/severity (Tables 2–6). TMAO production may also explain the inconsistent effects observed with fish, dairy products and poultry (all rich sources of choline). Interestingly, those eating primarily plant-based diets, with limited choline/phosphatidylcholine and L-carnitine ingestion, do not seem to produce significant quantities of TMAO, even after ingestion of L-carnitine/choline[113].

Limitations

The focus here was on associations between dietary pattern, dietary components as well as nutrients and HF risk/severity. Therefore, evidence focused on salt/Na or fluid restriction,

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micronutrient supplementation, alcohol, over-/undernutrition as well as animal/cell model data was omitted.

The literature searches and the data presented here focus on HF. However, HF is related to multiple cardiometabolic risk factors and disorders. It is possible that factors influencing these processes may also influence HF incidence/severity. However, a comprehensive review of nutritional factors contributing to HF and non-HF cardiometabolic perturbations is outside the scope of this review. Further, there are many HF manifestations, for example, preserved *v.* reduced ejection fraction. It is possible that different HF manifestations may require different dietary approaches. However, data specific to specific HF manifestations are limited.

Many studies reviewed herein included only one measurement of dietary intake or blood nutrient level. These studies cannot determine whether participants changed their diet during the follow-up. Additionally, many of these studies assessed dietary intake via self-report (for example, FFQ). On the other hand, some studies directly measured blood nutrient level or microbiome metabolites but did not assess dietary intake. Therefore, the possibility of reverse correlation cannot be ruled out.

It is important to recognise that grouping categories of similar foodstuffs together can influence observations. For example, two prospective studies reported no association between consumption of nuts and HF incidence[60,119]. However, neither of these studies collected information on nut type. However, roasted and salted groundnuts may have a less favourable effect than raw, unsalted walnuts. Similarly, another prospective study reported that sweetened beverages were associated with HF risk[120]. However, this study did not differentiate between sugar-sweetened beverages and artificially-sweetened beverages. Finally, type and preparation of fish appear important[64].

Most available data are observational. Although retrospective, cross-sectional and prospective studies each have their strengths, flaws remain. Although the reported observations could be real, residual confounding by measured and unmeasured factors is a major concern, despite adjusted analysis. Caution with over-adjusting for confounding factors in dietary studies is recommended. For example: if red meat is associated with HF and diabetes and the results adjust for diabetes, then the association between HF and red meat diminishes. However, it is possible that red meat contributes to HF through increased diabetes risk.

Many reports included here were re-analysis involving the same cohorts. Although many of these studies were large and prospective, they often enrolled limited cohorts, for example, the Physicians' Health Study enrolled male physicians who were mostly Caucasian.

In the context of other CVD and HF precursors (for example, hypertension, obesity, diabetes) there is a notable lack of interventional trials regarding HF. Further, many existing intervention studies were pilot studies with small samples and short follow-up. Nevertheless, existing interventional trials of plant-based diets in HF have reported improvements in cardiac function, functional capacity and quality of life (Table 6), inferring a remarkable response. Based on consistent evidence of CVD benefit, the DASH diet was formally adopted into American College of Cardiology/American Heart Association CVD guidelines[28].

Future recommendations

The potential role of nutrition in HF prevention/treatment was first suggested in 1996[30]. The field has grown since then but remains limited, with many unanswered questions. It is recommended that future studies take account of type of HF and severity as well as pharmacological treatments and co-morbidities. Further, it is recommended that adequately powered sample sizes and relevant follow-up periods are utilised in investigator-blinded, randomised and controlled trials.

Conclusion

There is growing evidence that nutrition is a critical factor in the incidence and progression of HF. The existing but limited observational and interventional evidence from human studies suggests that a plant-based diet rich in fruit, vegetables, legumes and whole grains is likely to be beneficial, acting through multiple pathways.

Considering the relative safety and cost of dietary intervention combined with the limited knowledge on HF and diet, clinical trials are urgently needed to help elucidate the effect of dietary patterns/components on HF incidence/severity. This has been highlighted in the strategic plan of a joint National Institutes of Health and National Heart, Lung, and Blood Institute working group.

A seminal 1999 editorial[121] regarding the famous Lyon Diet Heart Study stated 'relatively simple dietary changes achieved greater reductions in risk of all-cause and coronary heart disease mortality in a secondary prevention trial than any of the cholesterol-lowering studies to date'. This editorial details the cost-effectiveness and high benefit:risk ratio of dietary manipulation compared with 'drugs and invasive procedures' and concludes that 'dietary factors must be very important'. Diet does seem important and I quote a more recent, expert editorial: 'in our search for the silver bullet, we have overlooked the silver plate. It is regrettable that we remain so imprecise and ill-informed about a cornerstone in patient care. Diet is important. We can and should know more'[7]. Physicians, dietitians, scientists, funding agencies and others are urged to help conduct further research in this crucial area.

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