ABSTRACT

Introduction The evidence on predictive value of lifestyle behaviours and dietary pattern on the prognosis of heart failure (HF) is limited. Our aim is to identify these factors in the setting of secondary prevention of HF.

Methods and analysis The Metabolic Abnormalities, Lifestyle and Dietary Pattern in Heart Failure study is an ongoing, prospective cohort, single-centre study that aims to recruit 1500 patients with HF from June 2016 to June 2021. At baseline, each participant completes a questionnaire on demographic characteristics, medical history, lifestyle behaviours, sleep duration and quality, bowel movements and regular diet. Biochemical measurements, blood pressure, carotid ultrasound, echocardiography, electrocardiography and cardiac magnetic resonance are obtained and analysed. Muscle strength is assessed using the handgrip dynamometer and the MicroFet2 hand-held dynamometer. Each patient is followed for 5 years or until the occurrence of death. The primary outcome is a composite of cardiovascular mortality or hospitalisation due to worsening heart failure. The secondary end points are cardiovascular deaths and the hospitalisations due to worsening HF. The incidence of mortality and cardiovascular events is documented biennially.

Ethics and dissemination The study protocol has been approved by the Ethics Committee of the Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, and follows the norms of the World’s Association Declaration of Helsinki. The results of this study will be disseminated in peer-reviewed journals and academic conferences.

Trial registration number NCT03951311.

BACKGROUND

Heart failure (HF), manifested as structural and functional cardiac abnormalities, is an end result of other cardiovascular diseases (CVD). Although pharmacological and device therapies have substantially reduced the death rate of CVD, the prognosis of patients with HF remains poor. Patients with HF are burdened by decreased quality of life, re-hospitalisation and CVD mortality. Unhealthy lifestyle behaviours (eg, tobacco use, heavy alcohol drinking and physical inactivity) and poor diet quality (eg, high intake of sugar-sweetened beverages and red and processed meats) are important risk factors for CVD. Dietary intervention and physical activity are effective in reducing the risk of metabolic diseases and CVD. For instance, vigorous physical activity is helpful to attain blood pressure and glucose target accompanied by commonly used antihypertensive/diabetic drugs. Healthy eating patterns, such as the Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet, have been recommended to reduce the risk of coronary artery diseases and metabolic abnormalities in the general population. However, previous studies of the association between these dietary patterns and HF and left ventricular dysfunction yielded mixed results. Constipation, defined as infrequent bowel movements and difficulties
during defecation, is a consequence of unhealthy diet (eg, low fibre diet) and physical inactivity. Constipation is associated with age, diabetes mellitus, hypertension and a lack of exercise, which are risk factors for CVD. A previous study found constipation was associated with the increased risk of HF. However, it is unclear about the contribution of constipation and dietary patterns to the prognosis of HF.

Sarcopenia is characterised by low muscle strength and impaired muscle function. Patients with HF are generally old to very old with limited exercise capacity in daily life; thus, sarcopenia is highly prevalent among patients with HF. Exercise training is considered beneficial to preventing the loss of muscle mass and muscle function. Previous studies found an inverse association of exercise with chronic subclinical myocardial damage and left ventricular hypertrophy. However, other studies found that high intensity interval training was not superior to moderate continuous training in improving left ventricle remodelling or aerobic capacity in patients with HF.

Regular exercise training based on standard therapy might have a non-significant or modest clinical benefit to improve HF survival and re-hospitalisation; and the safety of vigorous physical activity in patients with HF, especially in those with advanced age or multiple comorbid conditions is still unclear. We therefore conduct a prospective cohort study to assess the association of metabolic abnormalities, lifestyle behaviours and dietary patterns with HF prognosis.

PATIENTS AND METHODS

Study cohort

The Metabolic Abnormalities, Lifestyle and Dietary Pattern in Heart Failure (MALD-HF) study is an ongoing prospective cohort study embedded into the Ruijin Hospital (Shanghai, China). Recruitment begins from June 2016 to June 2021. We aim to include a total of 1500 Chinese patients with HF. Participants are recruited consecutively according to the following inclusion criteria:

1. aged 14 years or older;
2. typical symptoms of HF according to the Framingham criteria; 
3. left ventricular ejection fraction (LVEF) <50%, demonstrated by echocardiography or cardiac magnetic resonance, which include either patients with mid-range EF (HFmEF) or with reduced EF (HFrEF) with relevant structural and functional cardiac changes and/or elevated N-terminal pro-brain B-type natriuretic peptide BNP (pro-BNP) (eg, ≥400 pg/mL); 
Exclusion criteria include: 
1. age <14 years or ≥90 years; 
2. pregnancy; 
3. cancer with a life expectancy of <1 year; 
4. participation in other trials; 
5. endocarditis, pericardial diseases or congenital heart diseases; 
6. HF secondary to non-cardiac diseases (eg, pulmonary heart disease, infection, infiltration, metabolic derangements, severe anaemia, sepsis and arteriovenous fistula); 
7. lack of informed consent and (8) refusal of the drug treatment or intervention recommended by the guidelines.

Each patient with HF is asked to finish a standardised questionnaire about demographic characteristics, medical history, lifestyle behaviours and regular diet. If the patients cannot complete the questionnaire or are unable to respond, their relatives or those who are familiar with their characteristics are accepted as respondents.

The main exposures include food composition, lifestyle behaviours, muscle strength, biological parameters and metabolic factors, defined as shown in table 1. Patients with HF are considered as having a family history of CVD if at least one of their first-degree relatives has that disease. The frequency and amount of tobacco smoked per day and years since smoking cessation are recorded. Furthermore, the information on alcohol consumption includes drinking frequency, type of alcoholic beverage and volume of alcohol consumed on a typical drinking day (figure 1).

Ethics and dissemination

Ethical approval

The study protocol has been approved by the Ethics Committee of the Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, and follows the norms of the World’s Association Declaration of Helsinki. All patients with HF recruited in the MALD-HF study give their informed consent at the time of enrolment.

Dissemination

The results of this study will be disseminated in peer-reviewed journals and academic conferences.

Sample size estimation

We use data of previous cohort studies of lifestyle behaviours in patients with chronic HF to determine the sample size. The sample size is calculated with the estimate of an 25.9% mortality in patients with HF without alcohol consumption, the estimate of an 37% mortality in patients with HF without exercise prescription. Assuming a 5% loss to follow-up, a two-sided alpha level of 0.05, we calculate that the study will have >80% power to detect a 20% reduction in mortality with a total number of 1500 patients, using the two-sided Z test. If the sample size cannot be fulfilled during the study time frame, the recruitment period will be extended. Sample size calculations are performed using PASS 15 (NCSS, Kaysville, Utah, USA).

Left ventricular structure and function

Left ventricular structure and function (eg, left ventricular mass, end-systolic/diastolic volume, mass-to-volume ratio, stroke volume and ejection fraction) and carotid intima-media thickness are measured using a high-resolution tomographic ultrasonic system (ACUSON SC2000, Siemens, Munich, Germany) after admission. The ejection fraction is calculated as the end-systolic volume divided by the end-diastolic volume multiplied by 100%, according to Simpson’s rule. A repeat echocardiography is performed after 12–24 months in participants.
who have received one at baseline. A 12-lead electrocardiography is then used to diagnose arrhythmia.

Assessment of dietary pattern
We ask about lifestyle behaviours and dietary habits in the baseline questionnaire. The dietary pattern is assessed by a self-administered semi-quantitative Food Frequency Questionnaire (FFQ) that has been validated in previous studies. This FFQ includes 14 food components commonly consumed in China: oils/fats, fruits, vegetables, nuts, legumes, fish and seafood, dairy products, whole grains, sodium, sweets, sweetened beverages, potatoes, meats and eggs. Each participant is asked about the frequency (never, number of times per day, per week, per month or per year) and the amount of each food consumed with the aid of food-size reference photographs. The average intake of each item per day is calculated by multiplying the frequency per day by the amount consumed at each time. The daily energy intake of participants is calculated according to the China Food Composition Database.

Assessment of physical activity
The baseline physical activity status is assessed using the International Physical Activity Questionnaire (IPAQ)-Form previously validated. Each participant is asked about the type, frequency and duration of each activity, such as occupation, transportation, housework and recreational activity per day/week in the past year: vigorous activity (eg, running, cycling, tennis, callisthenics, aerobics, swimming or heavy working), moderate activity (eg, housework or Tai Chi), light activity (eg, walking) or sedentary activity (eg, sitting or lying awake). The IPAQ-Form data are converted to metabolic equivalent scores×minutes per week for each type of activity according to the IPAQ guideline for data processing and analysis.

Table 1 Baseline visits and follow-ups

| Measure                                                                 | Baseline | Biennial follow-up |
|------------------------------------------------------------------------|----------|-------------------|
| Demographic information (sex, age, nationality, marriage, education, monthly salary, occupation) | ✓        |                   |
| Disease history (eg, MI, CAD, cardiomyopathy, valvular heart disease)  | ✓        | ✓                 |
| Intervention (eg, PCI, CABG, CRT/ICD, valvular surgery, TAVI, ventricular aneurysm surgery) | ✓        | ✓                 |
| Arrhythmia (atrial/ventricular premature beats, atrial flutter, atrial fibrillation, ventricular tachycardia, sick sinus syndrome, atrioventricular block) | ✓        | ✓                 |
| Medication history (eg, aspirin, P2Y12 inhibitors, ACEI/ARB/ARNI, β-blocker, CCB, statins, diuretic, aldosterone receptor antagonist, digoxin, amiodarone) | ✓        | ✓                 |
| Comorbidity (hypertension, diabetes mellitus, dyslipidaemia, stroke, chronic kidney disease, thyroid disease, pulmonary diseases) | ✓        | ✓                 |
| Family history of cardiovascular diseases or metabolic abnormalities  | ✓        |                   |
| Dietary pattern (eg, food type, food frequency and flavour)            | ✓        |                   |
| Lifestyle behaviours (eg, tea, coffee and alcohol consumption)         | ✓        |                   |
| Sleep duration, sleep quality, the use of sleeping pills              | ✓        |                   |
| Muscle function and strength (eg, SARC-F questionnaire, handgrip and limb muscle strength) | ✓        | ✓                 |
| Bowel movements (eg, stool frequency, constipation and the use of laxative) | ✓        |                   |
| Physical activity (eg, exercise type, exercise frequency and exercise duration) | ✓        |                   |
| Physical examination (eg, height, weight, waist and hip circumference and blood pressure) | ✓        |                   |
| HF symptoms (acute/chronic HF, Killip class, NYHA class, nausea/vomiting and oedema) | ✓        | ✓                 |
| Cardiac imaging test (coronary angiography/electrocardiography, echocardiography and cardiac magnetic resonance) | ✓        | ✓                 |
| Chest CT, vascular ultrasonography, ABI, PWV                           | ✓        |                   |
| Blood biochemical parameters (WBC, RBC, platelets, glucose and insulin, HbA1c, lipid profile, creatinine and uric acid, pro-BNP, thyroxine, interleukin, hs-CRP, myocardial enzymes, tumour necrosis factor, tumour markers, ferritin) | ✓        |                   |
| Urine sample (urine protein, microalbuminuria, creatinine and albumin/creatinine) | ✓        |                   |

ABI, ankle brachial index; ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCB, calcium channel blocker; CRT, cardiac resynchronisation therapy; HbA1c, haemoglobin A1c; hs-CRP, high-sensitivity C reactive protein; ICD, implantable cardioverter-defibrillator; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; pro-BNP, pro-brain natriuretic peptide; PWV, pulse wave velocity; RBC, red blood cell; TAVI, transcatheter aortic valve implantation; WBC, white blood cell.
Assessment of bowel movements
Patients with HF are asked to provide information on the parameters of bowel movements (eg, stool frequency, straining during defecations) and use of laxatives. The functional constipation is assessed according to the Rome IV criteria.34

Assessment of sleeping duration and quality
The information on sleep parameters (eg, sleep duration, sleep quality and snoring) is collected via questionnaires that have been previously used.35 There are six indicators of sleep quality: (1) delayed sleep induction after turning-off the lights; (2) awakening during the night; (3) early final awakening and difficulty getting back to sleep; (4) use of sleeping drugs; (5) sleepiness at daytime as to need a nap; (6) unsatisfactory sleep quality in the morning. We construct a sleeping score based on the six indicators. Each indicator is scored from 0 to 3 (0=never, 1=1–2 times per week, 2=3–4 times per week, 3=≥5 times per week). Snoring is defined in this study as snoring plus breathing stops (>10s).36 Information on snoring and breathing stop is obtained in the absence of the symptom of dyspnoea or via asking spouses of patients with HF or those who take care of them daily. The frequency and severity of snoring are also noted. A home-sleeping test device (Alice NightOne, Philips, Amsterdam, The Netherlands) is used to determine the presence of sleep apnoea and the duration of apnoea.

Assessment of sarcopenia and muscle strength
Sarcopenia is diagnosed based on the SARC-F questionnaire including five components: strength, assistance with walking, rise from a chair, climbing stairs and falls; the scores range from 0 to 2 points for each component. A score ≥4 is considered as sarcopenia.37 Arm strength is analysed using the handheld dynamometer, and limb muscle strength is assessed using the MicroFet2 handheld dynamometer that has been verified to be reliable.
for measuring muscle strength. A mean of two measurements is used in each of the arm-strength and limb-strength tests.

**Assessment of ankle brachial index and pulse wave velocity**

Ankle brachial index (ABI) and pulse wave velocity (PWV) are measured using an automatic device (Colin, Komaki, Japan). Patients with HF receive ABI/PWV measurements by trained nurses in the morning without tea or coffee in a controlled temperature between 22°C and 24°C, following the manufacturer’s recommendations. ABI is calculated by dividing ankle systolic blood pressure (SBP) by the brachial SBP, while PWV is estimated as a proxy of arterial stiffness based on the European Expert Consensus on Arterial Stiffness.

**Assessment of biological parameters**

Fasting blood samples for biochemical parameters are collected within 24 hours of hospital admission. Blood glucose, lipid profiles (eg, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides and lipoprotein (a)), electrolytes, iron, albumin, creatinine and urine protein are analysed using commercial kits (AU5800; Beckman Coulter, USA). Myocardial enzymes, tumour markers and ferritin are analysed using luminescence immunoassay methods (DXI-800-1; Beckman Coulter). Blood cells (eg, white blood cell, red blood cell or platelets) are analysed using the Unicel DxH 800 Blood Analyzer (Beckman Coulter); NT-pro-BNP is analysed using the Cobas e601 Biochemical Autoanalyzer (Roche, Switzerland); high-sensitivity C reactive protein is measured using the Cobas c311 Biochemical Autoanalyzer (Roche). Inflammatory factors (eg, interleukin (IL)-1β, IL-6, IL-10, tumour necrosis factor-α) are tested by flow cytometry (FACSCanto II; BD Bioscience, USA). The interassay coefficient of all variables is below 10%. Estimated glomerular filtration rate is calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation considering creatinine, sex and age. The single, random, midstream morning urine samples are measured using a urine analyzer for microalbuminuria and urine albumin-creatinine ratio (AU5800; Beckman Coulter). Diabetes mellitus is defined as a fasting blood glucose concentration ≥7.0 mmol/L, a non-fasting glucose ≥11.1 mmol/L or self-reported use of glucose-lowering drugs.

**Assessment of clinical parameters**

SBP and diastolic blood pressure (DBP) represent the means of three duplicate measures conducted after individuals have been seated quietly for at least 5 min using an electronic sphygmomanometer (HBP-1300, OMRON). Hypertension is defined as SBP ≥140 mmHg, DBP ≥90 mmHg or self-reported use of BP-lowering drugs according to the Seventh Joint National Committee. Waist circumference and hip circumference are measured using a tape rule, both to the nearest 0.1 cm in the absence of oedema. Waist-to-hip ratio is calculated by dividing waist circumference in centimetres by hip circumference in centimetres. Height and weight are measured using a calibrated platform scale, to the nearest 0.1 cm and 0.1 kg. The dry-weight body mass index (BMI) is calculated by dividing dry weight in kilograms by the square of height in metres.

**Assessment of outcomes**

All participants are followed for up to 5 years after the index procedure. The primary outcome is a composite of cardiovascular mortality or hospitalisation due to subjectively and objectively worsening HF. The main cause of death is coded based on International Classification of Diseases-10th Revision. The secondary end points are cardiovascular deaths (sudden death or deaths due to CVD events) and the adjudicated hospitalisations due to worsening HF. An independent committee of experts including three physicians reviews all the death certificates and medical records for adjudicating the death cases and all suspected CVD cases biennially from the index episode, via telephone contacting patients’ family members or reviewing medical records and the Hospital Discharge Register data.

Specifically, myocardial infarction is diagnosed based on cardiac symptoms, positive cardiac biomarkers or electrocardiography. Ischaemic stroke and haemorrhagic stroke are defined as neurological deficits of cerebrovascular cause that last >24 hours or a significant lesion detected by CT or MRI.

**Patient and public involvement**

No patient will be involved in the protocol design or implementation of the study.

**Statistical analysis**

The person-time for each patient with HF is accumulated from the finishing date of the baseline survey to date of whichever event comes first: death or termination of follow-up. Baseline characteristics of patients with HF are summarised using mean±SD or medians with IQRs for continuous variables and frequencies or percentages for categorical variables. The HR with 95% CI is analysed by Cox proportional regression, adjusting for baseline characteristics that strongly predict the clinical outcomes (eg, age, sex, lifestyle behaviours, hypertension/blood pressure, diabetes mellitus/glucose, lipid profiles, renal function index, inflammatory biomarkers and N-terminal pro-BNP). The test for interaction between two covariables will be performed by using likelihood ratio test comparing models with and without cross-product term. HF aetiology (eg, dilated cardiomyopathy, hypertrophic cardiomyopathy or ischaemic cardiomyopathy) is prespecified as a stratification factor. As for missing data, the distributions of clinical characteristics are compared in those with complete and incomplete data. The more preferred approach to missing data is multiple imputation. The missing values are replaced by imputed
values selected at random from the predictive distribution based on the observed data by the regression model. In addition, the main competing risks are non-CVD deaths. The cumulative incidence function method and the Fine-Gray subdistribution hazards model are used to estimate the competing hazards for the primary outcome and death from non-CVD causes. Statistical analyses are performed using STATA V12.0 (StataCorp, College Station, Texas, USA), and a two-sided p value <0.05 is considered statistically significant.

DISCUSSION

The MALD-HF study is designed to investigate the predictive value of metabolic abnormalities, lifestyle behaviours and dietary pattern for HF prognosis, because previous studies concerning the effect of lifestyle and diet interventions in the secondary prevention of HF yielded conflicting or obscure results. One of the aims of the MALD-HF study is to fill this knowledge gap by focusing on lifestyle and dietary patterns that may aid the prediction of HF deterioration.

Exercise training has been considered useful for preventing the occurrence of HF. The 2019 American College of Cardiology/American Heart Association guideline on the primary prevention of cardiovascular disease recommended at least 150 min of moderate-intensity physical activity per week or 75 min of vigorous-intensity physical activity per week in the general population. Individuals with severe HF, however, have a lower exercise tolerance than healthy people and more often cannot attain the recommended period and intensity of physical activity. A previous small study (n=242) found that Tai Chi, a low-intensity physical activity derived from China, significantly improved the quality of life but did not confer the change in N-terminal-pro-BNP, SBP and 6 min walking distance in patients with HF, suggesting a necessity for a properly designed exercise training to patients with HF.

The adherence to different dietary patterns may have different influences on the risk of HF. For example, in the Women’s Health Initiative participants with HF (n=3215), the DASH diet scores modestly predicted post-HF mortality while there was a non-significant trend towards an inverse association between the Mediterranean diet scores and post-HF mortality. Caloric restriction improved exercise capacity, metabolic abnormality and left ventricular function in older people with obesity without HF, but it was controversial in patients with HF. Low-carbohydrate and high-protein diets seemed to improve the functional capacity in patients with HF, but there is no evidence for reduction of CVD events in patients with HF. The dietary pattern of Chinese people is different from that of Western people. For example, Chinese adults consume more highly refined grain, legumes and rapeseed oils, and less milk and olive oil compared with Western people. Our FQ has been validated for reliability in Chinese people and used for the Chinese national nutrition survey in 2010. The results are expected to reflect the dietary habits of Chinese patients with HF and will contribute the knowledge for the dietary guidance individually designed for them.

Sleep-disordered breathing (eg, apnoea and hypopnoea) is common in patients with HF. It is still unclear whether sleep-disordered breathing is a consequence or causally associated with poor HF prognosis. The evidence on the treatment of obstructive sleep apnoea using positive airway pressure conferring survival benefit is still lacking. We will propose to assess the sleeping quality and apnoea by constructing a sleeping score to provide more information on guidance for lifestyle intervention to improve HF prognosis.

The current study still has several limitations. First, the anticipated sample size is moderate (n=1500), which may limit the power to perform a detailed classification. Second, we do not include patients with preserved EF (HFPekEF) in our study because there is lacking precise indicators and objective one-method-fit-all approach for diagnosing HFPekEF and the false-positive and false-negative diagnosis cannot be avoided. Patients with increased left ventricular-filling pressure may not have the increased concentrations of BNP and the echocardiographic variables for diagnosing diastolic dysfunction are limited, which challenges the current criteria diagnosing HFPekEF in clinical practice. In addition, HFPekEF is secondary to heterogeneous pathophysiological phenotypes and affected by these comorbidities (eg, age and obesity), which makes it difficult to identify unique risk factors at play in HFPekEF. Further extensive studies investigating population with special HFPekEF phenotypes (eg, atrial fibrillation-related HFPekEF or obesity-related HFPekEF) may help to elucidate the association between lifestyle behaviours/dietary pattern and HFPekEF prognosis. Third, this is a single-centre study, and all the assessments of imaging data and blood samples are performed in the same hospital without validation of interinstitutional variation. Thus, we cannot completely exclude the potential bias due to measurements. Fourth, the assessments of dietary pattern, lifestyle behaviours and sarcopenia are self-reported. Although the questionnaire is valid and reliable, the potential recall bias could not be completely removed. Nevertheless, we use a home-sleeping test device and a hand-held dynamometer for the objective measurements of apnoea and muscle strength. Fifth, the findings from our study may not be generalisable to all those excluded herein (eg, right ventricular failure, endocarditis or cardiomyopathy in children).

In summary, the MALD-HF study is an ongoing study recruiting HF survivors with the aim of investigating the association between metabolic abnormalities, lifestyle behaviours, dietary pattern and HF prognosis. The results will improve our understanding of the predictive value of these risk factors in the setting of secondary prevention of HF.
REFERENCES

1. McMurray JJV, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology, developed in collaboration with the heart failure association (HFA) of the ESC. Eur Heart J 2012;33:1787–847.

2. Buddeke J, Valstar GB, van Dis I, et al. Mortality after hospital admission for heart failure: improvement over time, equally strong in women as in men. BMC Public Health 2020;20:36.

3. GBD 2016 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2016: a systematic analysis for the global burden of disease study 2016. Lancet 2017;390:1345–422.

4. Arnett DK, Khera A, Blumenthal RS. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: Part 1, lifestyle and behavioral factors. JAMA Cardiol 2019;4:1043–4.

5. Naci H, Salcher-Korndorff M, Dias S, et al. How does exercise treatment compare with antihypertensive medications? A network meta-analysis of 391 randomised controlled trials assessing exercise and medication effects on systolic blood pressure. Br J Sports Med 2019;53:859–69.

6. Lanthers C, Walther G, Chapier R, et al. Long-term cost reduction of routine medications following a residential programme combining physical activity and nutrition in the treatment of type 2 diabetes: a prospective cohort study. BMJ Open 2017;7:e013763.

7. American Heart Association Nutrition Committee, Lichtenstein AH, Appel LJ, et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American heart association nutrition committee. Circulation 2006;114:82–96.

8. de Lorgeil M, Renaud S, Marnelle N, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. Lancet 1994;343:1454–9.

9. Estruch R, Martinez-Gonzalez MA, Corella D, et al. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. Ann Intern Med 2006;145:1–11.

10. Levitan EB, Ahmed A, Arnett DK, et al. Mediterranean diet score and left ventricular structure and function: the multi-ethnic study of atherosclerosis. Am J Clin Nutr 2016;104:595–602.

11. Gardener H, Rundek T, Wright CB, et al. A Mediterranean-style diet and stroke risk: a meta-analysis. JAMA 2015;115:514.

12. Tektonidi TG, Åkesson A, Gigante B, et al. A Mediterranean diet and risk of myocardial infarction, heart failure and stroke: a population-based cohort study. Atherosclerosis 2015;243:93–8.

13. Foxx-Orenstein AE, McNally MA, Ounsted MA, et al. Exercise and the cardiovascular system: clinical science and cardiovascular outcomes. Circ Res 2015;117:207–19.

14. Campanini MZ, Guallar E, Artalejo F, et al. Mediterranean diet score and left ventricular structure and function: a systematic review of factors that improve mortality and morbidity. Am J Cardiol 2020;115:2129–200.

15. Sundboll J, Szepietowski SK, Aellenborg K, et al. Constitution and risk of cardiovascular diseases: a Danish population-based matched cohort study. BMJ Open 2020;10:e037080.

16. von Haseling S, Lainscak M, Doehner W, et al. Diabetes mellitus, cachexia and obesity in heart failure: rationale and design of the studies investigating co-morbidities aggravating heart failure (SICA-HF). J Cardiovasc Med 2010;1:187–94.

17. Bezkaf T, Pellicci P, Morris DA, et al. Sarcopenia in patients with heart failure with preserved ejection fraction: impact on muscle strength, exercise capacity and quality of life. Int J Cardiol 2016;222:41–6.

18. Koste A, Visscher M, Simonsick EM, et al. Association between fitness and changes in body composition and muscle strength. J Am Geriatr Soc 2010;58:219–26.

19. Florido R, Ndumele CE, Kwak L, et al. Physical Activity, Obesity, and Subclinical Myocardial Damage. JACC Heart Fail 2017:5:377–84.

20. Kamimura D, Loprinzi PD, Wang W, et al. Physical activity is associated with reduced left ventricular mass in obese and hypertensive African Americans. Am J Hypertens 2017;30:617–23.

21. Ismail H, McFarlane JR, Nojoumian AH, et al. Clinical outcomes and cardiovascular responses to different exercise training intensities in patients with heart failure: a systematic review and meta-analysis. JACC Heart Fail 2013;1:514–22.

22. Lavi CJ, Arena R, Swift DL, et al. Exercise and the cardiovascular system: clinical science and cardiovascular outcomes. Circ Res 2015;117:207–19.

23. Piepoli MF, Davos C, Francis DP, et al. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). BMJ 2004;328:189.

24. Smart N, Marwick TH. Exercise training for patients with heart failure: a systematic review of factors that improve mortality and morbidity. Am J Med 2004;116:693–706.

25. Siscovick DS, Weiss NS, Fletcher RH, et al. The incidence of primary cardiac arrest during vigorous exercise. N Engl J Med 1984;311:874–7.

26. McKeep PA, Castelli WP, McNamara PM, et al. The natural history of congestive heart failure: the Framingham study. N Engl J Med 1971;285:1441–6.

27. Ponikowski P, Voors AA, Anker SD. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;2016:2129–200.

28. Cooper HA, Exner DV, Domanski MJ. Light-to-moderate alcohol consumption and prognosis in patients with left ventricular systolic dysfunction. J Am Coll Cardiol 2000;35:1753–9.

29. Doukky R, Mangia A, Ibrahim Z, et al. Impact of physical inactivity on mortality in patients with heart failure. Am J Cardiol 2016;117:1135–43.

30. Sacket DL, RW, Rosenberg W. Evidence-Based Medicine: how to practice and teach EBM. New York: Churchill Livingstone, 1997.

31. He Y, Li Y, Yang X, et al. The dietary transition and its association with cardiometabolic mortality among Chinese adults, 1982–2012: a cross-sectional population-based study. Lancet Diabetes Endocrinol 2019;7:540–8.

32. Liu D, Zhao L-Y, Yu D-M, et al. Dietary patterns and association with obesity of children aged 6–17 years in medium and small cities in China: findings from the CHNS-2010–2012. Nutrients 2016;11.3.

33. Craig CL, Marshall AL, Sjøstrøm M, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35:1381–95.

34. Mearin F, Ciriza C, Minguez M, et al. Clinical practice guideline: irritable bowel syndrome with constipation and functional constipation in the adult. Rev Esp Enferm Dig 2016;108:332–63.

35. Campanini MZ, Gualar-Castillón P, Rodríguez-Artalejo F, et al. Mediterranean diet and changes in sleep duration and indicators of sleep quality in older adults. Sleep 2017;40: doi:10.1093/sleep/zsw083. [Epub ahead of print, 01 Mar 2017].

36. Li J, Huang Z, Hou J, et al. Sleep and CKD in Chinese adults: a cross-sectional study. Clin J Am Soc Nephrol 2017;12:885–92.

37. Malmström CK, Morley JE. SARCO-F: a simple questionnaire to rapidly diagnose sarcopenia. J Am Med Dir Assoc 2013;14:531–2.

38. Conceição A, Parraca J, Marinho D, et al. Assessment of isometric strength of the shoulder rotators in swimmers using a handheld dynamometer: a reliability study. Acta Bioeng Biomech 2018:20:113–9.

39. Van Bortel LM, Lauren S, Boutouyrie P, et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. J Hypertens 2012;30:445–8.
40 Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–12.

41 American Diabetes Association. Clinical practice recommendations 2005. *Diabetes Care* 2005;28 Suppl 1:S1–79.

42 Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *JAMA* 2003;289:2560–72.

43 Tunstall-Pedoe H, Kuulasmaa K, Amouyal P, et al. Myocardial infarction and coronary deaths in the world Health organization MONICA project. registration procedures, event rates, and case-fatality rates in 28 populations from 21 countries in four continents. *Circulation* 1994;90:583–612.

44 Stroke--1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. *Stroke* 1989;20:1407–31.

45 Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2203.

46 Wolbers M, Koller MT, Witteman JCM, et al. Prognostic models with competing risks: methods and application to coronary risk prediction. *Epidemiology* 2009;20:555–61.

47 JP F, RJ G. A proportional hazards model for the Subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509.

48 Arnett DK, Blumenthal RS, Albert MA. ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American heart association Task force on clinical practice guidelines. *J Am Coll Cardiol* 2019;73:177–232.

49 Pan L, Yan J, Guo Y, et al. Effects of Tai Chi training on exercise capacity and quality of life in patients with chronic heart failure: a meta-analysis. *Eur J Heart Fail* 2013;15:316–23.

50 Levitan EB, Lewis CE, Tinker LF, et al. Mediterranean and DASH diet scores and mortality in women with heart failure: the women’s health initiative. *Circ Heart Fail* 2013;6:1116–23.

51 Villareal DT, Chode S, Parimi N, et al. Weight loss, exercise, or both and physical function in obese older adults. *N Engl J Med* 2011;364:1218–29.

52 Kitzman DW, Brubaker P, Morgan T, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA* 2016;315:36–46.

53 Wang J, Lin X, Bloomgarden ZT, et al. The Jiangnan diet, a healthy diet pattern for Chinese. *J Diabetes* 2020;12:365–71.

54 Vazir A, Hastings PC, Dayer M, et al. A high prevalence of sleep disordered breathing in men with mild symptomatic chronic heart failure due to left ventricular systolic dysfunction. *Eur J Heart Fail* 2007;9:243–50.

55 Kasai T, Narui K, Dohi T, et al. Prognosis of patients with heart failure and obstructive sleep apnea treated with continuous positive airway pressure. *Chest* 2008;133:690–6.

56 Schelbert EB, Frielman Y, Wong TC, et al. Temporal relation between myocardial fibrosis and heart failure with preserved ejection fraction: association with baseline disease severity and subsequent outcome. *JAMA Cardiol* 2017;2:995–1006.

57 Cheng RK, Cox M, Neely ML, et al. Outcomes in patients with heart failure with preserved, borderline, and reduced ejection fraction in the Medicare population. *Am Heart J* 2014;168:721–30.

58 Gruden G, Landi A, Bruno G. Natriuretic peptides, heart, and adipose tissue: new findings and future developments for diabetes research. *Diabetes Care* 2014;37:2899–908.

59 Yancy CW, Jessup M, Bozkurt B. ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American heart association Task force on clinical practice guidelines and the heart failure Society of America. *J Card Fail* 2017;23:628–51.

60 Shah AM, Solomon SD. Phenotypic and pathophysiological heterogeneity in heart failure with preserved ejection fraction. *Eur Heart J* 2012;33:1716–7.