DIABETES MANAGEMENT IN HEART FAILURE

by

YUTA ISHIKAWA

(Under the Direction of Elisabeth Lilian Pia Sattler)

ABSTRACT

Heart failure (HF) patients are at risk of new-onset type 2 diabetes because of heightened insulin resistance resulting from compensatory mechanisms of cardiac dysfunction. Patients with coexisting HF and diabetes face increased risks of morbidity and mortality in comparison to patients with HF alone which makes the early identification and management of type 2 diabetes among HF patients important. The objectives of this dissertation were to 1) assess prevalence and trends of type 2 diabetes and prediabetes among HF patients in the U.S. (study 1, chapter 3), to 2) compare diagnostic methods for type 2 diabetes among HF patients in the U.S. (study 2, chapter 4), and to 3) examine the association between the Dietary Approaches to Stop Hypertension (DASH) diet adherence and insulin resistance among HF patients in the U.S. (study 3, chapter 5). In study 1, more than 85% of HF patients showed signs of hyperglycemia: prevalence estimates of diagnosed, undiagnosed type 2 diabetes, and prediabetes among HF patients were 34.7%, 12.8%, and 39.1%, respectively. Prevalence estimates of diagnosed type 2 diabetes were significantly different between non-Hispanic whites (20.1% [95% CI, 13.5-27.6%]) and Hispanics (52.1% [95% CI, 35.9-68.0%]) ($P < 0.001$). The prevalence of type 2 diabetes and prediabetes did not significantly change between 2005 and 2016. In study 2, we found the concordance in diabetes case detection among diagnostic methods for diabetes to be limited: hemoglobin A1c (HbA1c) alone identified only 27.0%, whereas the 2-hour plasma glucose after oral glucose tolerance test alone identified 70.5% of cases. We found that the currently recommended HbA1c cutoff point of 6.5% would have left 76% of diabetes cases in our sample undiagnosed. In study 3, we observed that HF patients with the highest DASH adherence, in comparison to those with the lowest DASH adherence, showed 77.1% lower odds of having the highest level of insulin resistance (odds ratio: 0.229 [95% CI: 0.073-0.716]; p = 0.017 for linear trend). In conclusion, emphasis needs to be placed on the prevention and early diagnosis of new-onset type 2 diabetes among HF patients to reduce the individual and societal burden.

INDEX WORDS: Heart failure, Type 2 diabetes, Prediabetes, Insulin resistance,
Cardiovascular epidemiology, Secondary prevention, Diabetes tests,
Dietary Approaches to Stop Hypertension diet

DIABETES MANAGEMENT IN HEART FAILURE

by

YUTA ISHIKAWA

B.S., Kyoto Prefectural University, Japan, 2012

M.P.H., Louisiana State University Health Sciences Center, New Orleans, 2017

A Dissertation Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment of the Requirements for the Degree

DOCTOR OF PHILOSOPHY

ATHENS, GEORGIA

2021

DIABETES MANAGEMENT IN HEART FAILURE

by

YUTA ISHIKAWA

Major Professor:	Elisabeth Lilian Pia Sattler
Committee:	Alex Kojo Anderson Emma Monkhouse Laing Donglan Zhang

Electronic Version Approved:

Ron Walcott
Vice Provost for Graduate Education and Dean of the Graduate School
The University of Georgia
December 2021

ACKNOWLEDGEMENTS

I would like to express my gratitude to my major professor Dr. Elisabeth L. P. Sattler, who always encouraged me to aim high and gave me tremendous support throughout my doctorate degree program. I am so appreciative of your generosity with your time to help me overcome many challenges that I have faced as an international doctoral student, and you always treated me like a true family member. I am forever proud of being your first doctoral student.

I would like to thank my advisory committee members, Drs. Alex K. Anderson, Emma M. Laing, and Donglan “Stacy” Zhang for their guidance and constructive feedback. Dr. Anderson, you were always willing to share your time and expertise to advance my professional development. Dr. Laing, you always welcomed me with open arms to motivate and keep me uplifted in my dissertation studies. Dr. Zhang, you have taught me the many lessons regarding statistical analyses of complex sample survey data.

I am forever grateful for the love, support, and encouragement of my family, Emiko, Akira, Mari, and Sakura, and friends and colleagues, Rupal Trivedi-Kapoor, Ryo Tamura, Kota Banzai, Mai Spaulding, Yura Son, Julie Heejin Jeon, Gissel Ferriol, Oskar Pérez, Drs. Richard D. Lewis, Joseph M. Kindler, Arshed A. Quyyumi, Sandra B. Dunbar, Tung-Sung Tseng, Melissa K. Melby. Especially my parents have shown me a great understanding of studying outside of my home country and never held me back from pursuing my dream.

Finally, I would like to thank Mariko, my wonderful wife, for her love and support. You have always encouraged and inspired me throughout my doctorate degree program. You have always been my strength. I cannot wait to begin our next journey together!

TABLE OF CONTENTS

Page

CHAPTER

APPENDICES

LIST OF TABLES

Page

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

Problem Statement

Heart failure (HF) is a chronic and progressive disease caused by structural and functional impairment of ventricular filling and ejection of blood (1) and represents one of the leading causes of morbidity and mortality in the Western world (2). An estimated 6.2 million American adults lived with HF during 2013-2016 (3), and the number is projected to increase by 46% in 2030, which is equal to over 8 million American adults (4). This increasing trend can be primarily attributed to the aging of society and improved survival after myocardial infarction because of medical advances over past decades (5). Epidemiological and clinical data have demonstrated that coexisting HF and type 2 diabetes are highly prevalent, ranging between 10% and 47% (6, 7). A meta-analysis of 38,000+ patients with coexisting HF and type 2 diabetes showed increased risks of all-cause mortality, cardiovascular mortality, and hospitalizations compared to those with HF alone (8). Thus, the coexistence of HF and type 2 diabetes predisposes to an increased individual and societal burden due to increased healthcare costs (9).

Historically, clinicians have thought of diabetes as a risk factor in the development of HF. This has been supported by observational studies which reported individuals with diabetes to have a 2- to 4-fold increased risk of developing new-onset HF in comparison to those without diabetes (6). The mechanism underlying the development of HF among patients with type 2 diabetes was first suggested by Rubler in 1972, who described diabetic cardiomyopathy as myocardial diastolic dysfunction with structural and functional changes that diabetic individuals develop in the absence of coronary artery disease, valvular disease, or other conventional cardiovascular risk factors, such as hypertension and dyslipidemia (10). As a consequence, clinicians and public health officials have traditionally focused on the primary and secondary prevention of HF among type 2 diabetes patients (11).

During the global epidemic of type 2 diabetes (12), the directionality of the causal relationship between type 2 diabetes and HF has received significant attention (6, 7). Growing epidemiological and clinical evidence sheds light on the bidirectional association of the two chronic conditions: While diabetes is a known risk factor for the development of HF, HF patients are at risk of new-onset type 2 diabetes as well (13-15). Heart failure pathophysiology and medication-induced nutrient imbalances give rise to insulin resistance, resulting in a 1.7-fold higher risk of developing new-onset type 2 diabetes among HF patients, compared to individuals without HF (16). Previously, prevalence rates of type 2 diabetes among HF patients were estimated from selected in- and outpatient populations in clinical trials and registries and showed a wide range of estimates between 10% to 47% (6, 7). Although few population-based studies estimated prevalence rates and trends of type 2 diabetes among HF patients, their estimates were derived from predominantly non-Hispanic white majority populations (17-23). Thus, more diverse, nationally representative prevalence and trend estimates of type 2 diabetes among HF patients, and the sociodemographic and health characteristics of HF patients at risk of developing type 2 diabetes, are needed. Such new evidence facilitates the development of targeted clinical guidance for the prevention and management of both coexisting conditions.

Previous studies suggested limited concordance among evidence-based diagnostic methods for diabetes, as recommended by the American Diabetes Association, including hemoglobin A1c, fasting plasma glucose, and 2-hour plasma glucose after oral glucose tolerance test, in populations with coronary artery disease and acute coronary syndrome (24-27). There is currently limited understanding of the clinical performance of diagnostic measures of diabetes among HF patients. Because using a diagnostic method with low sensitivity likely delays identification and treatment of diabetes and consequently put HF patients at increased risks of morbidity and mortality, an investigation into the appropriateness of diagnostic measures for diabetes in this population is needed.

Lastly, adherence to healthy dietary patterns, such as the Dietary Approaches to Stop Hypertension (DASH) diet, has shown to improve insulin resistance in clinical trials with individuals without established HF (28-30). However, it is currently unclear whether adherence to the DASH diet shows beneficial effects on insulin resistance among HF patients without a prior diagnosis of diabetes that are similar to those observed among non-HF patients (28-30). It is important to fill these gaps in knowledge and to raise awareness among researchers, clinicians, and policymakers of strategies needed to address type 2 diabetes prevention among HF patients.

Purpose of Dissertation Research

The purpose of this dissertation research is to 1) assess the burden of type 2 diabetes among HF patients and 2) to provide evidence that may assist in the improved prevention of type 2 diabetes among HF patients. The specific objectives of this dissertation are to 1) assess the prevalence and trends of type 2 diabetes, including diagnosed and undiagnosed type 2 diabetes and prediabetes, among U.S. community-dwelling adults with HF, 2) compare diagnostic methods for diabetes among U.S. community-dwelling adults with HF, and 3) examine the association between the Dietary Approaches to Stop Hypertension (DASH) diet adherence and the severity of insulin resistance among U.S. community-dwelling HF patients without diabetes.

Dissertation Overview

This dissertation consists of 6 chapters. Chapter 1 introduces the gaps in research related to the coexisting conditions of type 2 diabetes and HF and describes the purpose of the dissertation research.

Chapter 2 contains a review of the literature related to the following dissertation-relevant topics: 1) definition and classification, pathophysiology, epidemiology, and clinical significance of HF, 2) definition and classification, pathophysiology, and epidemiology of type 2 diabetes, 3) pathophysiology, epidemiology, and clinical significance of coexistence of HF and type 2 diabetes and the degree of accordance among diagnostic methods for diabetes, 4) unintended consequences of HF medications on HF outcomes among patients with coexisting HF and diabetes, 5) potential effects of hypoglycemic medications on HF outcomes among HF patients with diabetes, 6) energy imbalance and nutritional deficiencies among HF patients, 7) medical nutrition therapy for diabetes and effects of healthy eating patterns, including Mediterranean, DASH, and plant-based dietary patterns, on diabetes-related outcomes, 8) effects of nutritional status, medication therapy, sodium restriction, adherence to healthy dietary patterns, and nutritional supplementation on HF outcomes.

Chapters 3-5 contain 3 original research articles in manuscript format. The work presented in Chapter 3 is entitled "Prevalence and Trends of Type 2 Diabetes Mellitus and Prediabetes among Community-Dwelling Heart Failure Patients in the United States", which is a secondary analysis of National Health and Nutrition Examination Survey (NHANES) data aimed at assessing the prevalence and trends of type 2 diabetes and prediabetes among community-dwelling HF patients in the U.S. Chapter 4 describes a project entitled "Comparison of Diagnostic Methods for Diabetes in Patients with Heart Failure: A National Health and Nutrition

Examination Survey Analysis”, which is a cross-sectional study using NHANES data to examine the degree of agreement among hemoglobin A1c, fasting plasma glucose, and 2-hour plasma glucose after oral glucose tolerance test for diabetes identification among HF patients. Chapter 5 presents a project entitled “High Adherence to the Dietary Approaches to Stop Hypertension Diet is Associated with Low Levels of Insulin Resistance among Community-Dwelling Heart Failure Patients: A National Health and Nutrition Examination Survey Analysis”, which was a cross-sectional study of 1999-2016 NHANES data which aimed to examine the association between the DASH diet adherence and insulin resistance among HF patients. Chapter 6 concludes the dissertation study findings and provides recommendations for future research directions.

CHAPTER 2

LITERATURE REVIEW

Introduction

Heart failure (HF) represents one of the leading causes of morbidity and mortality in developed countries (2). Epidemiological and clinical data show that coexisting HF and type 2 diabetes are highly prevalent (31). Cardiovascular diseases are the primary cause of mortality in patients with diabetes (32), and it is estimated that the risk of HF in men and women with diabetes increases 2-fold and 5-fold compared to their counterparts without diabetes, respectively (33). This may be explained by advanced glycation end products, created by non-enzymatic reactions between glycating compounds and lipids/proteins, causing microvascular damages, which result in increased vascular disease risk (34). Thus, type 2 diabetes has traditionally been considered as a risk factor for developing new-onset HF. Although HF development among diabetes patients has received more attention in the past, growing epidemiological and clinical evidence suggests that the association between diabetes and HF might be bidirectional: HF patients may be at high risk of developing new-onset type 2 diabetes as well (13-15). This literature review discusses the clinical significance of HF and diabetes, the pathophysiological mechanisms underlying diabetes development among HF patients, and effects of pharmacological and nonpharmacological approaches on diabetes and HF outcomes, with particular focus on nutrition. In addition, this literature review defines gaps in current research and underlines the importance of the present dissertation research.

Heart Failure

Definition and Classification of Heart Failure

Heart failure is a chronic and progressive syndrome characterized by structural or functional impairment of ventricular filling and ejection of blood (1). The classification of HF can be based on a) the time of onset, b) the location of the myocardial impairment, c) the functional status of ventricular ejection fraction, and d) cardiac output (35). Based on the time of onset, HF is classified as acute or chronic. Acute HF shows a rapid onset of new (de novo) HF or sudden worsening (decompensation) of signs and symptoms of HF, while patients who have previously experienced HF and are currently stable are referred to as having chronic HF (36). The impairment of the myocardium can occur at the left, the right, or both ventricles, but most patients with HF experience symptoms due to a deficit of the left ventricular myocardial function (35). The clinical status of left ventricular ejection fraction (LVEF; %) classifies patients into two categories: heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF). The definition of HFrEF varies among guidelines and have been defined as LVEF $\leq$ 35%, < 40%, and $\leq$ 40% (36-38). Patients with HF are classified as HFpEF if LVEF is $\geq$ 50%, and they are further classified as borderline HFpEF if the LVEF is between 41% and 49% (37). Patients with HF may also be classified by cardiac output (35). Cardiac output can be measured by a resting cardiac index based on the volume of blood pumped by the heart and the body surface area, and patients with high-output failure show an elevated resting cardiac index (> 2.5-4.0 L/min/m^2) and lower systemic vascular resistance. Low-output failure shows insufficient cardiac output and is more common than high-output failure. In addition to clinically defined classifications, the American College of Cardiology/American Heart Association (ACC/AHA) staging system and the New York Heart Association (NYHA) functional classification are used to describe the severity of HF (37). The ACC/AHA staging system defines 4 stages of HF based on the development and progression of HF; Stage A: At high risk for HF but without structural heart disease or symptoms of HF; Stage B: Structural heart disease but without signs or symptoms of HF; Stage C: Structural heart disease with prior or current symptoms of HF; Stage D: Refractory HF requiring specialized interventions (37). The NYHA functional classification defines 4 classes based on the exercise capacity and symptomatic status of HF; Class I: No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF; Class II: Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF; Class III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF; Class IV: Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest (37).

Diagnosis of Heart Failure

A diagnosis of HF is confirmed using various parameters: laboratory assessment (complete blood count, urinalysis, serum electrolytes, blood urea nitrogen, serum creatine, glucose, fasting lipid profile, liver function tests, thyroid-stimulating hormone, and natriuretic peptides), noninvasive cardiac imaging techniques (chest X-ray; transthoracic echocardiography, TTE; computerized tomography scans, CT scans; magnetic resonance imaging, MRI; and 12-lead electrocardiogram, 12-lead ECG), and/or invasive evaluation (a pulmonary artery catheter, invasive hemodynamic monitoring, coronary arteriography, and endomyocardial biopsy) (37). Natriuretic peptides, including brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), both of which are secreted in response to volume expansion and pressure overload, are used to support a clinical judgment of HF diagnosis in both in- and outpatient settings (37). For example, a single measurement of natriuretic peptide (BNP ≤ 100 pg/ml or NT-proBNP ≤ 300 pg/ml) clinically excludes HF (39). Chest X-rays are used to 1) examine heart size and pulmonary congestion, and 2) identify alternative cardio-pulmonary diseases. Results of TTE are used to assess 1) left ventricular systolic/diastolic function, 2) right ventricular function, and 3) pulmonary artery pressure (37). Cardiac CT scans can accurately assess cardiac structure and function, including of the coronary arteries (36). Cardiac MRI assesses 1) volumes, mass, and ejection fraction of both the left and right ventricles and 2) myocardial infiltration or scar (36). A 12-lead ECG is useful to 1) determine heart rhythm, heart rate, QRS morphology, and QRS duration (36). Invasive evaluation is recommended when a clinical assessment is inadequate and/or hemodynamics are uncertain. A diagnosis algorithm of HF can vary depending on the time of onset (36). Patients with suspected acute HF are first examined if they have cardiogenic shock and/or respiratory failure during the urgent phase after first medical contact. If they have these symptoms, the patients receive circulatory or ventilatory support for immediate stabilization and will be transferred to an intensive care unit (ICU)/critical care unit (CCU). If they have neither cariogenic shock nor respiratory failure or their symptom becomes stabilized after ICU/CCU, patients with suspected acute HF are then examined to identify an acute etiology, following an immediate initiation of specific treatment if necessary and clinical evaluation to confirm acute HF with laboratory assessment and cardiac imaging techniques. In non-acute settings, patients with suspected HF will receive a comprehensive assessment, including clinical history, physical examination, ECG, natriuretic peptides, and echocardiography, to confirm HF and identify its etiology.

Pathophysiology of Heart Failure

Pathophysiological changes in HF begin when compensatory mechanisms for ventricular impairment attempt to maintain adequate cardiac performance. Compensatory mechanisms include the Frank-Starling mechanism, activation of neurohormonal pathways, and cardiac remodeling (40). The Frank-Starling mechanism involves adjustment of cardiac myocytes to its contraction force and stroke volume to the left ventricular end-diastolic volume (41). Thus, the afterload of the heart increases when cardiac output decreases to prevent congestion in the early stage of HF. The activation of neurohormonal pathways is the first response to impaired cardiac function, including the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system (RAAS), and natriuretic peptides (40). In impaired cardiac function, the effects of baroreceptors, the main inhibitors of the SNS, decrease while excitatory impulses increase. The imbalance between baroreceptors and excitatory impulses induces the activation of SNS, leading to increased cardiac contractility and rapid heart rates in order to redistribute blood in the body. Activated SNS thereupon stimulates the RAAS, resulting in the release of renin from the kidney and in the conversion of inactive pre-hormone angiotensinogen to angiotensin I. Angiotensin I is then converted to angiotensin II by angiotensin-converting enzyme, and angiotensin II induces vasoconstriction to regulate blood pressure and secretion of aldosterone from the adrenal cortex, increasing sodium and water reabsorption from the kidney into the blood. Activated SNS and RAAS provoke myocardial stretching by volume or pressure overload, and consequently release natriuretic peptides from the heart chambers. Released natriuretic peptides promote vasodilation and subsequent reduction in the atrial/ventricular fillings, as well as deactivation of SNS and RAAS (42, 43). Although the acute activation of neurohormonal pathways maintain cardiovascular homeostasis, the chronic activation will cause cardiac remodeling (44). Cardiac remodeling is defined as the structural and functional alteration in the heart, including changes of heart dimensions, mass, and shape in response to impaired cardiac function (45, 46). Progression of cardiac remodeling consequently leads to the enlargement of the heart (cardiomegaly), microstructural changes (e.g., cardiomyocyte hypertrophy, apoptosis, and necrosis), interstitial fibrosis, macrostructural changes (e.g., left ventricular hypertrophy), ventricular dilation, and left ventricular stiffness (40, 46). These pathophysiological changes contribute to increased inflammatory responses and oxidative stress in the heart, and eventually the wide spectrum of clinical manifestations in HF appear, including pulmonary manifestations (e.g., pulmonary congestion, dyspnea, orthopnea, cardiac asthma, Cheyne-stokes respiration etc.), anemia, edema, gastrointestinal symptoms, cardiac cachexia, renal failure, and cerebral symptoms (e.g., confusion, sleep disorders, dizziness, altered mood, disorientation, etc.) (47).

Prevalence and Incidence of Heart Failure in the U.S.

Heart failure is a highly prevalent and growing problem of public health significance. Particularly among older adults and non-Hispanic blacks, incidence rates of HF are high (3). An estimated 6.2 million American adults had HF during the period 2013-2016 (3), and the prevalence of HF is projected to increase by 46% in 2030, which is equal to over 8 million American adults (4). The age and gender stratified prevalence rates show that 12.8% of males and 12.0% of females aged 80+ years had HF, so did 6.9% of males and 4.8% of females aged 60-79 years (3). The incidence of HF is approximately 21 per 1,000 population among older Americans aged 65+ years (48). The age- and race-stratified incidence rates of acute decompensated HF show that non-Hispanic black males aged 75+ years had the highest incidence rate, in comparison to non-Hispanic black females, non-Hispanic white males, and non-Hispanic white females in the same age group (34.7, 31.4, 32.0, and 26.2 per 1,000 person-years, respectively) (3). In different age groups (55-64 and 65-74 years of age), non-Hispanic blacks, both male and female, showed higher incidence rates compared to their non-Hispanic white counterparts (3).

Significance of Heart Failure

The clinical manifestations of HF significantly impact individuals and society. In 2017, 80,480 reported mortality cases in the U.S. (43,656 females and 36,824 males) were attributed to HF (3). The HF mortality cases across racial/ethnic and gender groups varied as follows: 36,004 cases for females and 30,076 cases for males in non-Hispanic whites, 4,683 cases for females and 4,068 cases for males in non-Hispanic blacks, 752 cases for females and 633 cases for males in non-Hispanic Asians, and 1,960 cases for females and 1,820 cases for males in Hispanics (3). In addition, the 30-day, 1-year, and 5-year mortality rates after hospital discharges for HF were 10.4%, 22.0%, and 42.3%, respectively (49). Although survival after the onset of HF in older adults has improved over past years (50), the number of HF-related hospital discharges has increased in both males and females in the U.S. In 1997, approximately 1,750,000 (males) and 1,400,000 (females) HF-related hospital discharges occurred, while it reached 3,500,000 cases for both males and females in 2014 (51). Increased hospitalization rates contribute to increased total medical costs for HF, which was estimated to be $30.7 billion in 2012. About 80% of these costs were associated with hospitalizations (4). Because the elderly population is growing and this population is more likely to be hospitalized for HF complications compared to any other conditions (52), health care expenditures for HF are predicted to increase continuously (4). Under the Affordable Care Act in 2010, the Hospital Readmissions Reduction Program (HRRP), a financial incentive program to reduce healthcare expenditures for excess readmissions due to HF, acute myocardial infarction, and pneumonia among Medicare beneficiaries, was established and implemented in 2012 (53). After the implementation of HRRP, readmission rates for the targeted conditions declined nationwide (54, 55).

Type 2 Diabetes

Definition and Diagnosis of Type 2 Diabetes

Diabetes is a metabolic disorder characterized by hyperglycemia due to impaired insulin secretion, insulin action, or both (56). Diabetes can be classified into several categories based on the clinical circumstances at the time of diagnosis. Type 2 diabetes is characterized as relative insulin deficiency, which results from defective β-cell insulin secretion, impaired response to insulin stimulation of targeted tissues, or both (56). Patients with suspected type 2 diabetes receive a diagnostic test for diabetes using the following criteria: 1) fasting plasma glucose (FPG) ≥ 126 mg/dL, 2) hemoglobin A1c (HbA1c) ≥ 6.5%, 3) 2-hour plasma glucose (2hPG) after the oral glucose tolerance test (OGTT) ≥ 200 mg/dL, and 4) a random plasma glucose ≥ 200 mg/dL for a patient with classic symptoms of hyperglycemia or hyperglycemic crisis (56). Unless a patient meets a random plasma glucose ≥ 200 mg/dL, a second test is required for confirmation of diabetes using the same criteria. A second test is recommended to be performed either by repeating the same test on a different day or by a different test using a new blood sample on the same day as the first test. Although all diagnostic measures are considered to be equally appropriate for diabetes diagnosis, some discordance among these measures may exist (57).

Pathophysiology of Type 2 Diabetes

Type 2 diabetes is a chronic disease of impaired glucose metabolism, which involves a feedback loop between β-cell and insulin-sensitive tissues (58). In normal glucose metabolism among heathy individuals, insulin secretion in response to β-cell stimulation controls glucose uptakes by insulin-sensitive tissues while the tissues release feedback information to regulate their need for insulin (59). In contrast, impaired glucose metabolism in type 2 diabetes is characterized by insulin resistance, which occurs when insulin-sensitive tissues do not respond well to insulin in multiple organs, including skeletal muscle, adipose tissue, the liver, and the heart (60). Insulin resistance results from several mechanisms, including inflammation and inflammatory cytokine production (61). For example, interleukin-1β (IL-1β), a proinflammatory cytokine, reduces insulin sensitivity in peripheral tissues (62, 63) and induces insulin resistance in fat cells (64) and liver cells (65). In addition, increased levels of other inflammatory markers, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor (TNF)-α, are correlated with impaired insulin sensitivity, insulin signalizing, and β-cell function (66-69). When insulin resistance develops in insulin-sensitive tissues, it impedes the feedback loop and increases insulin secretion from β-cells to maintain glucose homeostasis (58). Over time, insulin secretion triggered by increased plasma glucose is gradually impaired or lost, resulting in hyperglycemia (70). The severity of hyperglycemia is determined by the magnitude of β-cell dysfunction, and therefore hyperglycemia tends to become more severe and more difficult to treat as the disease is progressing (71). Although type 2 diabetes cannot be fully cured once developed, early management of modifiable risk factors for type 2 diabetes can prevent or delay the development of type 2 diabetes. Black (72) and Piccolo et al. (73) have described conceptual frameworks of risk factors influencing type 2 diabetes development, including demographic, socioeconomic, genetic, behavioral, psychological, healthcare utilization, and clinical factors. The risk factors involve complex interactions and can have direct and/or indirect effects on type 2 diabetes development. Meanwhile, risk factor modification likely reduces the risk of developing new-onset diabetes (74, 75). Therefore, identification of modifiable risk factors in a high-risk population and early intervention are critical to diabetes management.

Prevalence of Type 2 Diabetes in the U.S.

Data from the 2016 National Health Interview Survey (NHIS) revealed that 21.0 million individuals aged 18+ years reported having type 2 diabetes, which resulted in an estimated 8.58% of U.S. adults who had type 2 diabetes (76). The rates varied by age, gender, race/ethnicity, and education level groups. Adults aged 65+ years had the highest prevalence of type 2 diabetes (19.62%), followed by those aged 45-64 years (11.03%), 30-44 years (3.29%), and 18-29 years (0.66%). Males showed a higher prevalence of type 2 diabetes than females (8.86% and 8.32%, respectively). Non-Hispanic blacks had the highest prevalence of type 2 diabetes (11.52%), followed by Hispanics, non-Hispanic whites, and non-Hispanic Asians (9.07, 7.99, and 6.89%, respectively). Individuals with less than high-school education level had the highest prevalence compared to those with high school and more than high school education (14.20, 9.99, and 6.89%, respectively).

Diabetes in Heart Failure

Prevalence of Diagnosed and Undiagnosed Diabetes in Heart Failure Patients

Diabetes is a common comorbidity in HF patients, and the prevalence of diagnosed diabetes varies depending on patient type (in- vs. outpatients) and ejection fraction status (HFrEF vs. HFpEF). In outpatient settings, approximately 20-30% of patients with HFrEF have a previous diagnosis of diabetes (19, 77-79). In inpatient settings, the Efficacy of Vasopressin Antagonism in Heart Failure Outcomes Study with Tolvaptan (EVEREST) study reported that 40% of inpatients with HFrEF had diabetes (80). The Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM) study included patients with both HFrEF and

HFpEF, and showed that 35% of participants with HFrEF and 40% of those with HFpEF had comorbid diabetes (81). In addition, the prevalence of HF patients with undiagnosed diabetes, defined as if they did not have a previous diagnosis of diabetes but had elevated levels of fasting glucose and HbA1c above clinical thresholds, was approximately 15-25% (9, 81-83). Because none of these studies differentiated types of diabetes, the understanding of the prevalence of type 2 diabetes among HF patients is limited.

Prognosis of Heart Failure in Patients with and without Diagnosed or Undiagnosed Diabetes

Both diagnosed and undiagnosed diabetes are associated with a poor prognosis among HF patients. Cohort studies following HF patients with and without diabetes showed that coexisting diabetes significantly increased risks of all-cause hospitalization (9, 84), hospitalization due to worsening HF symptoms (81, 85), all-cause mortality (9, 82, 84), and cardiovascular mortality (83, 85). The CHARM study showed that diabetes increased the risk of hospitalization due to worsening HF symptoms, all-cause mortality, and cardiovascular mortality in both reduced and preserved ejection fraction functional types (81, 86). In addition, HF patients with undiagnosed diabetes had an increased risk of hospitalization due to worsening HF symptoms, all-cause mortality, and cardiovascular mortality compared to HF patients without diabetes (83, 85). Although impaired glucose metabolism in diabetes is not a reversible condition, better glycemic control may lead to better prognosis among HF patients with diabetes. Ad-hoc analysis of the CHARM study showed that HbA1c levels elevated by only 1% increased hospitalization for worsening HF symptoms, cardiovascular mortality, and all-cause mortality in HF patients with diabetes (87). In addition, a cohort study of inpatients with acute HF showed that participants with elevated plasma glucose levels had 3-fold higher in-hospital mortality compared to those with normal plasma glucose levels (88). Therefore, the early diagnosis and subsequent treatment of diabetes are important to reduce patient burden, hospitalizations, and mortality.

Pathophysiology Underlying Diabetes Development in Heart Failure Patients

The pathophysiological changes caused by HF symptoms, including SNS activation, neurohormonal abnormalities, elevated proinflammatory cytokines production, and metabolic alterations, contribute to insulin resistance and consequently the development of type 2 diabetes among HF patients (89). Activated SNS and RAAS, as compensation for cardiac dysfunction, stimulate lipolysis and therefore increase plasma free fatty acid (FFA) concentration (90). Increased plasma FFAs predispose to hyperglycemia through inhibition of glycolysis (91, 92) and insulin-stimulated glucose uptake (93, 94), induce lipotoxicity (95), and boost production of reactive oxygen species (13). In addition, cardiac dysfunction and its compensatory mechanisms induce cardiac and systematic proinflammation and increased inflammatory cytokine production (e.g., IL-1β, IL-6, TNF-α, etc.) (96), which impair insulin sensitivity, insulin signaling, and β-cell function (62-69). These metabolic alterations lead to the development of insulin resistance, reduce the β-cell capacity for insulin secretion, and result in new-onset diabetes (89). Moreover, increased angiotensin-II, due to the RAAS activation and hyperinsulinemia, cause vasoconstriction and blood pressure elevation, but eventually lead to exhaustion of cardiac activities and aggravate HF symptoms (97). This sustained activation results in elevated neurohormonal activation and a vicious cycle of insulin resistance and type 2 diabetes development (13). The reported pathophysiological alterations in HF patients along with the epidemiological evidence imply that HF patients are at high risk for developing new-onset diabetes.

A strong body of evidence shows that the severity of insulin resistance in patients with HF is associated with age, body mass index, smoking, daily physical activity, levels of serum triglycerides and high-density lipoprotein cholesterol, LVEF, NYHA functional class, and etiology of HF (98, 99). However, the number of included variables in previous studies examining the association with insulin resistance in patients with HF were limited, and many of the previously identified factors associated with insulin resistance in non-HF populations have not been examined in patients with HF, including waist circumference, diet (intake of energy, total fat, saturated fat, carbohydrate, dietary fibers, micronutrients, alcohol; adherence to certain dietary patterns, such as the Dietary Approaches to Stop Hypertension (DASH) dietary pattern), psychological distress, sleep deprivation, and medication use (e.g., angiotensin-converting enzyme inhibitors, β-blockers, diuretics, corticosteroids, oral contraceptives, nicotinic acid, antipsychotic agent, etc.) (100-102).

Diagnostic Methods for Diabetes in Heart Failure Patients

While most studies performed to date relied on either FPG or HbA1c alone to identify HF patients with type 2 diabetes, growing evidence suggests that FPG and HbA1c measurements may have lower performance than 2hPG after OGTT for detecting new-onset diabetes in populations with cardiovascular diseases. In patients with myocardial infarction, a risk factor for HF, the performance of HbA1c in diagnosing diabetes is weaker than the performance of FPG, as shown by an area under the receiver operating characteristic (ROC) curve of 0.71 for HbA1c and 0.76 for FPG based on 2-hour OGTT (103). In patients with coronary artery disease and acute coronary syndrome without history of diabetes, an independent risk factor for HF (104), the recommended HbA1c cutoff point for a diagnosis of diabetes (≥ 6.5%) had low sensitivity at 16-29%, and an area under the ROC curve of HbA1c for the identification of patients with diabetes ranged from 0.48 to 0.73, suggesting insufficient accuracy for diagnosing diabetes. In addition, the discordance among these diabetes measures was reported among over 4,000 patients with coronary artery disease, showing FPG alone identified 75%, 2hPG identified 40%, and HbA1c alone identified 17% of cases, while only 7% of cases were identified by all three methods (24). Only 1 small study reported that 14 of 56 patients with chronic HF were newly diagnosed with diabetes, where a total of 11 patients (76%) were identified by 2hPG alone, 2 patients (14%) by FPG and 2hPG, and 1 patient (7%) by FPG alone (82). Consequently, FPG misdiagnosed 40% of HF patients with newly diagnosed diabetes, as confirmed by 2hPG after OGTT (82). The lower performance of FPG in diagnosing diabetes, in comparison to 2hPG, among HF patients may be explained by pathophysiological mechanisms underlying diabetes development in HF patients. Heart failure patients are vulnerable to insulin resistance and may develop glucose intolerance before developing impaired fasting glucose (105). In addition, the small observational study among chronic HF patients showed that none of the participants with newly diagnosed diabetes was identified by HbA1c (82). Under certain clinical conditions, HbA1c measurements can be affected and become less reliable, such as in anemia (106), which is highly prevalent among HF patients (107-109). The low performance of HbA1c in diagnosing diabetes among HF patients stem from a study with a small number of HF patients, therefore limiting the interpretation of observed effects in HF patients.

Unintended Consequences of Heart Failure Medications on Heart Failure Outcomes in Heart Failure Patients with Diabetes

Heart failure pharmacotherapy is essential for HF management. However, some HF medications may show reduced efficacy in preventing HF hospitalizations and mortality, and have unintended consequences in HF patients with diabetes (110). Angiotensin-converting enzyme inhibitors (111, 112) and angiotensin II receptor blockers (113, 114), both of which are used to lower blood pressure, increase blood flow to the heart, and reduce the heart's workload, have shown positive effects on HF hospitalization rates and mortality among HF patients without diabetes; however, this positive effect has not been found among HF patients with diabetes (115, 116). Aliskiren, a direct renin inhibitor, has shown severe side-effects among HF patients with diabetes, including an increased risk of renal dysfunction, hyperkalemia, stroke, and hospitalization (117, 118). Thiazide diuretics, used for reduced volume overload and reduced blood pressure, can have negative effects on vascular and glucose metabolic abnormalities, including endothelial dysfunction and elevated vascular oxidative stress (119), hyperlipidemia (120), insulin resistance (121), new-onset diabetes (122), activation of SNS (123) and RAAS (124). These unintended consequences negatively impact HF prognosis in HF patients with diabetes.

Effects of Hypoglycemic Medications on Heart Failure Outcomes in Heart Failure Patients with Diabetes

Several hypoglycemic medications have shown unintended negative consequences on HF-related morbidity and mortality in HF patients; therefore, careful consideration is required when choosing most adequate hypoglycemic medications for HF patients with diabetes. Heart failure patients requiring insulin treatment have shown increased mortality, compared to those not requiring insulin therapy (125). In addition, treatment with insulin was associated with increased risks of all-cause mortality among HF patients aged 75+ years (126). Thiazolidinediones, which are used for improving insulin resistance, may contribute to fluid retention (127, 128) and increased incidence of HF events regardless of any prior history of clinical HF (129, 130); therefore, clinical guidelines recommended avoiding use of thiazolidinediones in patients with NYHA class II-IV HF (37). Dipeptidyl peptidase-4 inhibitors, which are used for elevating insulin release stimulation, may increase the risk of cardiovascular events and worsen HF symptoms (131, 132) although retrospective cohort studies showed inconclusive results (133, 134). Glucagon-like peptide-1 receptor agonists, which are used for lowering HbA1c and weight while displaying a low risk of hypoglycemia, increase HF-related events and mortality in HF patients (135, 136). In contrast, sodium-glucose cotransporter-2 (SGLT2) inhibitors, which are used for increasing urinary glucose and sodium excretion, have shown to reduce cardiovascular mortality and HF hospitalization in HF patients with diabetes (137, 138). The latter study results may be explained by an increasing concentration of circulating ketone bodies as a result of reduced plasma glucose levels and increased lipolysis in adipose tissue (139), which might be used as alternative energy source in the presence of insulin resistance (140) and other hemodynamic effects, including reduced blood pressure, oxidative stress, arterial stiffness, and SNS activation (141).

Heart Failure and Nutrition

Heart failure and nutrition are strongly associated. Pathophysiological and clinical manifestations of HF and the effect of HF medications likely influence nutritional status and consequently HF prognosis. In HF, the activation of neurohormonal pathways, accompanied by systemic inflammation, may cause elevated total energy expenditure and catabolic/anabolic imbalance, leading to negative energy balance compared to healthy controls (142). In addition, systemic fluid overload, caused by impaired myocardial function and renal perfusion, induces nausea, loss of appetite, and early satiety (143), which result in reduced nutritional intake. Given the high prevalence of HF in older adults, age-related factors, including cognitive, physical and sensory dysfunction, medication interactions, social isolation, and low-socioeconomic status, also affect their nutritional status (144). In addition, reduction of nutritional intake and malabsorption due to gastrointestinal edema place HF patients at a high risk of micronutrient deficiencies, including vitamin B1, B2, B6, folate, vitamin C, D and E, calcium, magnesium, iron, selenium, coenzyme Q10, and creatine, some of which play an important role in energy synthesis (145-148). Furthermore, HF medication may have unintended consequences in micronutrient deficiencies. For instance, loop diuretics may promote micronutrient loss, including B vitamins, potassium, calcium, magnesium, and selenium through excessive urinary excretion (149). Given the imbalance between increased energy demand due to the hypercatabolism and reduced energy supply due to pathophysiological changes and subsequent outcomes (150), an estimated 50% of HF patients are subject to malnutrition, and 15% of them might develop cardiac cachexia (143), both of which are associated with increased mortality and hospitalization rates (151, 152). Because of nutritional deficiencies among HF patients, dietary management seems to be a promising solution. Nevertheless, randomized controlled trials examining the effects of nutritional interventions have shown inconclusive results (153), and, due to lack of evidence-based nutritional interventions, current HF guidelines have focused on sodium restriction alone (154). However, sodium restriction may be associated with a decline in intake of energy, macronutrients, and specific food groups (155, 156). Clinical trials are warranted to establish evidence of dietary approaches on malnutrition and clarify the role of sodium restrictions in dietary HF management.

Diabetes and Nutrition

Dietary management, including nutrition therapy, is an important pillar of diabetes management. The American Diabetes Association (ADA) recommends that patients with diabetes should be actively involved in self-management education and support (157, 158), and should receive individualized eating plans and medical nutrition therapy (MNT), provided by a registered dietitian nutritionist who is knowledgeable and skilled in giving diabetes-specific MNT (159). The ADA sets 4 goals of nutrition therapy for patients with diabetes: 1) to promote and support healthful eating patterns, emphasizing a variety of nutrient-dense foods in appropriate portion sizes, in order to improve overall health, achieve proper weight management, biomarker levels (glycemic, blood pressure, lipid, etc.), and delay or prevent diabetic complications; 2) to address individual nutrition needs considering personal and cultural preferences, health literacy, access to healthful foods, intention and ability to make behavioral changes, and barriers to change behaviors; 3) to maintain the pleasure of eating by providing nonjudgmental messages about food choices; and 4) to give practical tools for developing healthy eating patterns (160). There is currently no recommended calorie distribution of macronutrients in a meal, including carbohydrate, fat, and protein (160) and a variety of eating patterns is recommended for the diabetes management (161, 162). As an example of a healthy eating pattern, the ADA suggests Mediterranean (163, 164), DASH (165-167), and plant-based (168, 169) dietary patterns based on previous research showing positive results on diabetes management. Although low-carbohydrate eating patterns may improve glycemia and potentially reduce the need for antihyperglycemic medications for individuals with type 2 diabetes (170-172), low-carbohydrate meal plans are currently not recommended for certain populations, including those with renal disease and those taking SGLT2 inhibitors (173). As a practical tool for basic meal planning guidance, the ADA suggests using the diabetes plate method, which shows a visual guide to control portion sizes of a meal with an emphasis on low-carbohydrate (or non-starchy) vegetables (174). In addition, weight management and reduction are important for patients with diabetes who are overweight or obese. Although underlying mechanisms remain uncertain, the degree of obesity is associated with insulin resistance potentially due to 1) increased production of adipokines/cytokines, 2) dysmetabolic sequelae caused by ectopic fat deposition, and 3) mitochondrial dysfunction (175). Furthermore, obesity-induced insulin resistance contributes to abnormal β-cell mass and function (176, 177), eventually resulting in β-cell dysfunction (178). In contrast, maintaining weight loss for 5 years is associated with well-controlled glycemic and lipid levels among patients with diabetes (179). Dietary interventions, including meal replacement to reduce calorie intake (179-181), the Mediterranean dietary pattern (182), and low-carbohydrate meal plans (170) have shown short-term (1-2 years) benefits of weight loss among patients with diabetes. However, healthcare providers should consider needs, feasibility, and safety to conduct these interventions to patients with diabetes (180).

Nutrition as a Therapeutic Modality [1]

Heart failure is a systematic disorder that results from structural and functional impairments of the cardiac blood circulatory system. Despite the availability of novel diagnostic and treatment approaches, HF presents a significant cause of morbidity and mortality (183, 184). An estimated 6.2 million Americans aged 20+ years have HF, and by 2030, the prevalence of HF is predicted to increase by 46% (3). Older Americans are more often hospitalized for HF than for any other condition (52), and 43% of HF patients require 4+ hospital readmissions after diagnosis (3). Rates of 30-day, 1-year, and 5-year mortality after HF-related hospital discharges remain high at 10.4%, 22.0%, and 42.3%, respectively (3). Due to high healthcare utilization and cost of care, total medical costs associated with HF were about $30.7 billion in 2012 and are

---

[1] Ishikawa Y, Sattler ELP. 2021. Current Atherosclerosis Reports 17;23(4):13.

Reprinted here with permission of the publisher.

projected to increase to $70 billion by 2030 (4). Given the human and economic burden associated with the condition, low-cost strategies to improve HF outcomes are desperately needed. Because HF patients commonly experience nutritional imbalances and malnutrition, which have been linked to increased morbidity and mortality (185-187), nutrition intervention is a plausible approach to managing HF. However, dietary guidance has traditionally focused on sodium restriction alone; a recommendation for which the evidence base is controversial. This article (1) discusses associations of malnutrition, nutritional imbalances, and HF and (2) summarizes the most recent available evidence regarding nutrition as a therapeutic modality in HF. The majority of the published literature on effective HF therapy relates specifically to HFrEF, which is characterized by LVEF < 35-50% (36, 38, 188-191). In contrast, in HFpEF, LVEF remains at ≥ 50% in the presence of non-diastolic abnormalities in cardiovascular function (36, 38, 188-191). As a result, this review is predominantly concerned with research related to the nutritional management of HFrEF, unless it is specifically stated otherwise.

Malnutrition and Nutrition Imbalances in Heart Failure

Malnutrition

Malnutrition is a common manifestation in patients with HF, and the underlying pathophysiological mechanisms are multifactorial and heterogeneous. Dependent on the patient population and the criteria used for diagnosis, about 30 to 70% of HF patients show some level of malnutrition (143, 185). Malnutrition is more prevalent among patients with more severe HF, as assessed by the NHYA functional classification (192). Through complex interactions between neurohormonal activation, intestinal edema, anorexia, and an imbalance between anabolism and catabolism, direct and indirect pathogenic effects as part of HF progression lead to an overall energy deficit and malnutrition (150). Moreover, malnutrition may lead to a reduction of cardiac output and eventually predispose HF patients to complications, including higher rates of hospital (re)admissions and mortality (185-187). Chronic malnutrition, along with immunological and inflammatory disorders, may further place HF patients at increased risk of developing cardiac cachexia, characterized as unintentional edema-free weight loss through loss of muscle, fat, and bone mass, which is strongly associated with decreased health-related quality of life and increased mortality (193). Malnutrition among HF patients, mediated through intestinal edema-induced malabsorption and anorexia, often involves micronutrient deficiencies, including deficiencies of B vitamins, vitamin C, vitamin D, calcium, selenium, zinc, iron, and coenzyme Q10 (CoQ10) (145, 146, 194). Up to 75% of HF patients experience deficiencies in one or more micronutrients (195). Although insufficient dietary intake of micronutrients is frequently observed in the general elderly population (196), HF patients of any age are vulnerable to micronutrient deficiencies due to mechanisms other than insufficient dietary intake alone (197-202). Micronutrients are essential cofactors to cardiac metabolism and function and are involved in the regulation of endothelial function, neurohormonal activation, myocardial energy metabolism, vascular inflammation, and oxidative stress (194). Observational studies indicate that micronutrient deficiencies are associated with the severity of HF progression, as assessed by the levels of BNP, NT-proBNP, and LVEF, exercise intolerance, hospital (re)admissions, and mortality (194). Moreover, a multicenter prospective cohort study demonstrated that micronutrient deficiencies predicted HF outcomes, where HF patients in the high deficiency category, defined as deficiency in 7+ out of 17 evaluated micronutrients, showed a 2-fold increased risk of all-cause hospitalization and mortality compared to those with a lower number of or no deficiencies (203). Given the clinical impact of malnutrition on HF outcomes, monitoring of nutritional status should be a standard part of HF treatment.

Impact of Heart Failure Medication Therapy

Medications are the first-line approach for the management of HF; however, unique interactions between medications and nutrients likely have an effect on nutritional status through alterations in cell bioavailability, intestinal absorption, and urinary excretion of nutrients (149, 204, 205). Within existing HF pathophysiology, these can exacerbate macro- and micronutrient imbalances and malnutrition (206). Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, both RAAS inhibitors with proven benefits for HF morbidity and mortality, may induce hyperkalemia due to decreased renal potassium excretion and zinc depletion due to increased renal zinc excretion (204, 205). In addition, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers have shown to cause taste disturbances (207, 208), which can lead to reduced appetite and food intake. Loop, thiazide, and potassium-sparing diuretics, which are commonly used for congestion management in volume-overloaded patients, accelerate urinary excretion of micronutrients and have shown to cause deficiencies in B vitamins, folic acid, calcium, magnesium, potassium, zinc, and selenium (149, 204, 205). Furthermore, the use of beta-blockers is associated with the risk of developing hyperkalemia by minimizing potassium excretion and increasing reabsorption (149), and beta-blockers deplete CoQ10, which is essential for energy production, due to inhibition of CoQ10-dependent enzyme (209). Calcium-channel blockers alter potassium homeostasis: they increase serum potassium concentration at usual doses while significantly reducing serum potassium concentration at large doses (210), predisposing HF patients to hypokalemia, increased mortality, and (re)admissions (211). Covalent bonding between hydralazine and vitamin B6 may result in vitamin B6 deficiency (205). Lastly, digoxin may exacerbate renal elimination of vitamin B, magnesium, potassium, calcium, and phosphorus (204), whereas it may reduce dietary intake overall by causing iatrogenic anorexia (212). Minimizing adverse outcomes from these interactions is crucial for HF management and might be achievable through monitoring and personalizing intakes of these micronutrients in HF patients.

Obesity

Evidence from a meta-analysis shows a 40% increase in new-onset HF per 5-unit increment in body mass index (BMI) (213). Body mass index has shown to have a greater impact on the development of HFpEF than on HFrEF (214). The pathogenic effects of obesity on HF are multifactorial, involving alterations in cardiac structure, function, metabolism, and lipotoxicity, and indirect effects through an increase in predisposing risk factors, such as endothelial dysfunction, atherosclerosis, hypertension, diabetes, atrial fibrillation, and kidney disease (193, 215). Loss of 5-10% of body weight through lifestyle modification is recommended for individuals with BMI ≥ 25 kg/m^2 for HF prevention (216).

Despite the established role of obesity in HF development, observational studies show associations between increased BMI and better, not worse, prognosis among patients with established HF (217, 218), regardless of the subtype of HF (219). This observation is called the "obesity paradox" and has led to controversies regarding weight-loss recommendations among patients with HF (193). Several hypotheses were proposed to explain the underlying mechanisms, including increased total blood volume and cardiac output, increased protective cytokines, attenuated RAAS, high physical function with increased muscle mass and strength, and better health-seeking behaviors due to elevated levels of health consciousness among overweight and obese HF patients (149, 220-222). However, the relationship between obesity and improved HF prognosis needs to be interpreted with caution. Research from the Meta-analysis Global Group in Chronic Heart Failure reported that the association could be u-shaped in both subtypes of HF, with no beneficial survival effects for HF patients with BMI $\geq$ 35 kg/m^2 (219), and the positive association was not observed in subgroups of HF, including patients with diabetes (223). More recently, a meta-analysis confirmed beneficial effects of overweight and obesity on all-cause mortality among HF patients; however, a neutral effect of obesity on cardiovascular mortality was observed, and HF decompensation incidence was exacerbated among HF patients who were overweight or obese (224). Furthermore, a meta-analysis of clinical studies indicated that intentional weight loss of approximately 40 kg (88 lbs) following bariatric surgery is likely to reverse cardiac remodeling in obese patients without established HF (224). Well-designed randomized controlled trials (RCTs) are needed to examine the effect of weight loss safety and effectiveness among patients with HF, which has been emphasized by the Heart Failure Society of American Scientific Statement Committee (193).

Nutrition in the Treatment of Heart Failure

Sodium Restriction

Dietary sodium restriction is widely recommended for cardiovascular disease prevention based on evidence showing correlations among dietary sodium intake, hypertension, end-organ damage, and mortality (225, 226). In addition, human clinical studies demonstrated reduced blood pressure among normotensive and hypertensive populations after dietary sodium restriction (225). However, mechanisms explaining the differential effects of sodium restriction on outcomes in patients with and without HF are currently unclear. Currently, there is no consensus among experts on the exact level of dietary sodium restriction to be used in HF ($\leq$ 1,500-3,000 mg/day), and evidence quality ratings used in clinical guidelines show weak evidence support for such recommendation (36, 38, 188-191, 227-229). Randomized controlled trials showed that among hospitalized HF patients with impaired ejection fraction, blood pressure and heart rate were improved as a result of sodium restriction; however, congestion symptoms, the rate of hospital (re)admissions, and mortality were not changed (230-232). Among community-dwelling HF patients receiving outpatient care, RCTs were inconclusive regarding changes in the severity of HF symptoms, as assessed by the NYHA functional class, and health-related quality of life, as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ), when comparing levels of sodium intake (230). One hypothesis opposing sodium restriction in HF may be that decreased dietary sodium intake leads to low cardiac output, stroke volume, and renal perfusion, which subsequently increases neurohormonal activation (e.g., BNP, angiotensin II, aldosterone, plasma renin activity), proinflammatory cytokine levels (e.g., TNF-α and IL-6), and a reduction of anti-inflammatory cytokines (e.g., interleukin-10), resulting in cardiac remodeling, decompensation, and (re)admission (233, 234). Due to the weak evidence base supporting sodium restriction among HF patients, the ACC/AHA guideline for the management of HF downgraded the level of evidence for the sodium intake recommendation from class I (235) to class IIa (188). Other international guidelines categorize sodium intake recommendations as supported by low or limited levels of evidence (38, 189-191, 227-229), while the European Society of Cardiology guideline no longer recommends dietary sodium restriction (36). Adequately powered RCTs are needed to improve our understanding of the physiological effects of dietary sodium restriction on HF outcomes. Such studies should be stratified by subtype of HF (e.g., HFrEF vs. HFpEF), disease severity (e.g., NYHA class), HF-related comorbidities (e.g., diabetes and renal disease), and other patient characteristics (e.g., demographic, sodium-sensitivity) (188). Sodium restriction may not be the best therapeutic lifestyle target after all, because observational evidence shows poor diet quality, including inadequate intakes of energy, protein, fat, carbohydrate, thiamin, calcium, and zinc, among HF patients with low dietary sodium intake (155, 236). Mechanistically, high blood pressure, a contributing factor to HF pathophysiology, may be negatively affected by sodium density in relation to energy intake, especially among non-obese individuals (237). Lastly, recent interest has shifted away from focusing on the single micronutrient sodium and towards understanding the influence of the dietary pattern consumption, in the context of nutritional status, on HF outcomes. This approach is supported by the Academy of Nutrition and Dietetics evidence-based practice guideline which recommends individualized sodium restriction within the range of 2,000-3,000 mg/day for the dietary management of HFrEF (229).

Dietary Patterns

Plant-Based Diet

A significant amount of research supports the association between the consumption of plant-based diets and the prevention of obesity, hypertension, diabetes, and heart disease (238-240). A typical plant-based diet is rich in plant origin foods, including fruits, vegetables, whole grains, and nuts, while allowing limited intake of animal products (241). Observational and interventional studies found that plant-based diets may prevent new-onset HF (242-247). The REasons for Geographic and Racial Differences in Stroke (REGARDS) prospective cohort study, which had a median follow-up of 8.7 years and collected data on over 16,000 participants without prior history of coronary artery disease and HF, showed that individuals with the highest plant-based diet adherence, in comparison to individuals with the lowest plant-based diet adherence, reduced their risk of new-onset HF by 40% (242). In addition, the Swedish Mammography Cohort study, a population-based prospective cohort study with a mean follow-up of 12.9 years in over 34,000 women with no prior history of cancer and cardiovascular diseases, showed that greater consumption of fruits and vegetables was associated with a 20%

reduction in new-onset HF (243). In interventional trials conducted in patients at risk of new-onset HF, participants who consumed a plant-based diet that emphasized increased intake of complex carbohydrates and reduced intake of fat and animal-based protein along with other means of lifestyle modification (e.g., exercise and stress management) significantly reduced BMI, blood pressure, clinical biomarkers (e.g., total cholesterol, low-density lipoprotein-cholesterol, apoprotein B, c-reactive protein, and insulin) and improved on the frequency of cardiac events (e.g., angina, needs of revascularization), physical functional capacity, LVEF, and quality of life (244-247).

Although clinical feeding trials using plant-based diets as a treatment modality for patients with established HF are limited, several case report studies showed potential health benefits as a result of the diets. In patients with HFrEF (LVEF 20-35%), consuming a plant-based diet emphasizing increased consumption of whole foods and reduction of fat intake while eliminating consumption of animal products improved cardiac performance and function, including increased LVEF, stroke volume, lumen diameter at the left anterior descending coronary artery ostial stenosis lesion, and decreased left ventricular mass (248-250). In addition, these patients showed improvement in physical function capacity, glucose homeostasis, and adiposity (248, 249).

Dietary Approaches to Stop Hypertension Diet

The DASH diet is an example of a heart healthy, low-saturated fat diet with emphasis on vegetable, fruit, whole grain, nut, seafood, poultry, and low-fat dairy product intake. It limits intake of red and processed meat, sugars, and processed foods and limits daily sodium consumption to less than 2,300 mg or 1,500 mg (low sodium)/day (251). The DASH diet has shown to lead to reductions in blood pressure comparable to medication therapy in adults who were not taking antihypertensive medications and had average systolic and diastolic blood pressures of 160 mmHg and 80–90 mmHg, respectively (252). Moreover, meta-analyses of prospective cohort studies suggest a significant inverse relationship between the consumption of a DASH diet and the incidence of diabetes, cardiovascular disease, coronary heart disease, and stroke, as well as reduced risks of all-cause, cardiovascular-, and cancer-specific mortality among healthy populations (253, 254). In addition, meta-analyses of RCTs found individuals who are consuming a DASH diet to have significantly lowered systolic and diastolic blood pressure, total cholesterol, low-density lipoprotein, CRP, and insulin levels (102, 255, 256). Most importantly, DASH diet consumption has shown promising effects on HF-related pathophysiological mechanisms, quality of life, and mortality in patients with established HF (257-262). The Women's Health Initiative, a prospective cohort study with a median follow-up of 4.6 years, showed a 16% reduction in mortality among women with HF who consumed diets closest to the DASH diet pattern in comparison to those with the least adherence to the DASH diet pattern (257). Beneficial effects of DASH diet consumption on HF outcomes were reported in clinical trials as well. The Dietary Approaches to Stop Hypertension in Diastolic Heart Failure (DASH-DHF) pilot study tested the effects of consuming a DASH diet for 21 days on HF outcomes among 13 HFpEF patients. Consumption of a DASH diet for 21 days was associated with improvements in systolic and diastolic blood pressure, diastolic function, left ventricular and arterial system, oxidative stress, and cardiac energy metabolism (258-260). A RCT among 48 HF patients with NYHA functional classes I–III and left ventricular systolic or diastolic dysfunction demonstrated that patients who received the DASH diet intervention for 3 months improved exercise tolerance, as assessed by the six-minute walk test, and quality of life, as assessed by the Minnesota Living with Heart Failure Questionnaire, compared to those in a control group (261). Although the Geriatric OUt-of-hospital Randomized MEal Trial in Heart Failure (GOURMET-HF), a randomized controlled feeding trial using home delivery of sodium-restricted DASH meals, showed only trends towards improvements in quality of life and 30-day HF hospital readmissions between the DASH diet and usual care groups after 12 weeks of intervention, the authors acknowledged limitations in statistical power and difficulties with the recruitment of this study population (262). Given these promising results on HF risk factors and outcomes, larger, better-powered studies are needed.

Mediterranean Diet

Limited evidence suggests that the Mediterranean diet may improve HF prognosis among HF patients. The Mediterranean diet is characterized by high intakes of fruit, olive oil, and nuts; moderate intake of poultry and fatty fish; and limited intakes of alcohol, red and processed meats, dairy products, and sweets (263). The diet has been associated with a lower risk of cardiovascular events, including new-onset HF and HF mortality, among healthy (264) and high-risk populations (265). Among patients with established HF, the only available data stem from Women's Health Initiative data which showed that higher adherence to a Mediterranean diet was associated with a reduced risk of mortality among women with HF. However, the results were no longer statistically significant after adjusting for further covariates in their final model (257).

Nutritional Supplementation

Nutritional supplementation likely plays an important role in managing malnutrition and micronutrient deficiencies in HF patients; however, effective nutritional supplementation strategies are not well supported by the current literature (194, 266). Evidence from a meta-analysis of 5 RCTs in malnourished HF patients suggests some improvement of nutritional status and rates of hospital (re)admissions and mortality as a result of nutritional supplementation

(266). However, the included studies represented low- to moderate-quality evidence with small sample sizes and short follow-up periods. Moreover, the included studies used diverse HF populations (e.g., inpatient vs. outpatient), outcomes (e.g., anthropometric measurement, physical function, quality of life, (re)admission, or mortality), and nutritional supplementation strategies, such as oral nutritional supplements (ONS) with or without specific amino acids (e.g., branched-chain amino acids), the combination of conventional treatment and personalized nutritional intervention (diet optimization, specific nutritional recommendations, and ONS when needed), or the combination of ONS and resistance exercise. The need for more robust evidence to fill this knowledge gap has been emphasized by experts at the National Institutes of Health National Heart, Lung, and Blood Institute and the Office of Dietary Supplements (267).

Future Research

Large clinical feeding trials are needed to fill gaps in our understanding of nutrition as a treatment modality in HF, particularly while considering different etiologies (ischemic vs. non-ischemic), subtypes (HFrEF vs. HFpEF), and comorbidities, and within the context of pharmacotherapy. These trials are best conducted within the infrastructure of Clinical and Translational Science Alliances (CTSAs) which may be able to overcome the unique challenges associated with the recruitment and enrollment of elderly HF patients while facilitating innovative clinical and translational research across the USA. The 60 currently existing CTSA hubs are sponsored by the National Institutes of Health National Center for Advancing Translational Sciences and provide networks that foster essential infrastructure for and innovation in training and research to promote meaningful clinical and translational research (268).

Conclusion

Malnutrition and nutrition imbalances are common among HF patients because of complex pathophysiological mechanisms related to HF progression and medication therapy, which are predisposing patients to poor HF prognosis with significant morbidity and mortality. In the absence of high-quality evidence addressing poor HF outcomes in the context of nutritional imbalances, current dietary guidance for HF management places emphasis on sodium and fluid restriction alone; a recommendation that has recently been challenged due to effectiveness and safety concerns. Limited, yet promising clinical studies support a beneficial impact of plant-based and DASH dietary patterns on HF-related health outcomes, including hospital (re)admissions and mortality.

Gaps in Current Research on Diabetes Management in Heart Failure Patients

Adequate diabetes prevention and management strategies among HF patients are essential for safe and effective HF treatment aimed at improving HF prognosis and outcomes; however, there are several gaps in knowledge in this area. Previously reported prevalence data of HF patients with diagnosed and undiagnosed type 2 diabetes were limited to the inclusion of in- and outpatient HF patients of predominantly non-Hispanic white ethnicity, therefore limiting the generalizability of results to US adults (17-23). Prevalence and trends analysis of type 2 diabetes among HF patients in a nationally representative sample of community-dwelling individuals may help to recognize the severity and unmet needs of the population in question. In addition, previous evidence has questioned use of FPG and HbA1c to identify type 2 diabetes in patients with HF (82). Examining the adequacy of guideline-recommended clinical parameters for the diagnosis of diabetes for HF patients and the degree of discordance among diagnostic diabetes measures in this population may help in determining the need for clinical guidance specific to

HF patients and may therefore assist in improved early identification of type 2 diabetes in patients with HF. Finally, given that patients with coexisting HF and type 2 diabetes have increased risks of morbidity and mortality in comparison to patients with HF alone (9), cost-effective strategies to prevent or delay new-onset type 2 diabetes in HF patients are warranted. The ADA recommends the DASH diet as an example of healthy dietary pattens to prevent the development of type 2 diabetes (269), which has shown to improve insulin resistance in individuals without established HF in clinical trials (28-30). Compared to individuals without HF, HF patients suffer from multiple comorbidities, including neurohormonal abnormalities, metabolic, and immunological abnormalities (6), which may affect the way the DASH diet impacts HF and/or diabetes outcomes among HF patients. Therefore, it is currently unclear whether adherence to the DASH diet shows similar effects on insulin resistance among HF patients as observed among non-HF patients. A better understanding of associations of DASH diet consumption with insulin resistance in patients with HF may provide further evidence on beneficial effects of the prevention of diabetes among HF patients.

Summary

Heart failure patients are at high risk of developing new-onset type 2 diabetes. HF pathophysiology promotes insulin resistance and the development of type 2 diabetes, and coexistence of the two conditions has shown to be associated with increased hospitalization rates, mortality, and healthcare expenditures over those with HF alone. There is limited knowledge regarding epidemiology of diabetes and diabetes prevention in HF patients. Raised awareness of the clinical implications of the coexisting conditions is important to promote early identification and prevention of type 2 diabetes among HF patients and to understand the role healthy nutrition plays in the prevention of diabetes among HF patients. This dissertation 1) examined the prevalence of type 2 diabetes and prediabetes in U.S. community-dwelling adults with HF, 2) compared guideline-recommended diagnostic methods for diabetes among U.S. community-dwelling adults with HF, and 3) explored the association between the DASH diet adherence and the severity of insulin resistance among U.S. community-dwelling HF patients without diabetes.

CHAPTER 3

PREVALENCE AND TRENDS OF TYPE 2 DIABETES MELLITUS AND PREDIABETES AMONG COMMUNITY-DWELLING HEART FAILURE PATIENTS IN THE UNITED STATES [2]

---

[2] Ishikawa Y, Lewis RD, Laing EM, Anderson AK, Zhang D, Quyyumi AA, Dunbar SB, Trivedi-Kapoor R, Sattler ELP.

Submitted to Diabetes Research and Clinical Practice, 09/17/2021.

Note: The Diabetes Research and Clinical Practice recommends use of type 2 diabetes mellitus (T2DM). Thus, the term is intentionally used in this manuscript.

Abstract

Aims

This study estimated national prevalence and trends of diagnosed and undiagnosed type 2 diabetes mellitus (T2DM) and prediabetes among heart failure (HF) patients in the U.S.

Methods

This cross-sectional study included 527 participants aged 20+ years with a diagnosis of HF, using data from the National Health and Nutrition Examination Survey 2005-2016. We assessed prevalence estimates of diagnosed and undiagnosed T2DM, and prediabetes stratified by age-standardized sociodemographic and health characteristics. Trends of T2DM and prediabetes prevalence were examined using logistic regressions.

Results

Over 85% of participants showed signs of hyperglycemia. Prevalence rates of diagnosed and undiagnosed T2DM among HF patients were 34.7% (95% confidence interval (CI), 29.2-40.3%) and 12.8% (95% CI, 9.2-16.9%), respectively. Prediabetes affected 39.1% (95% CI, 33.6-44.9%) of HF patients. Prevalence estimates of diagnosed T2DM were significantly different between non-Hispanic whites (20.1% [95% CI, 13.5-27.6%]) and Hispanics (52.1% [95% CI, 35.9-68.0%]) ($P < 0.001$). The prevalence of T2DM and prediabetes did not significantly change between 2005 and 2016.

Conclusions

Prevalence rates of T2DM and prediabetes among community-dwelling HF patients in the U.S. remained high between 2005 and 2016. Prevention of and targeted intervention for T2DM among at-risk HF patients is needed, particularly among those of Hispanic origin.

Introduction

Scientific statements published recently by the Heart Failure Association of the European Society of Cardiology and the American Heart Association and Heart Failure Society of America emphasize the need to better understand the epidemiology, prevention, and management of coexisting heart failure (HF) and type 2 diabetes mellitus (T2DM) (6, 7).

Patients with coexisting T2DM and HF have particularly poor patient outcomes and accrue significantly higher healthcare costs compared to patients with either of the two conditions alone (270, 271). Heart failure pathophysiology gives rise to metabolic impairments and insulin resistance, resulting in abnormally high incidence rates of T2DM in this population (272, 273). A meta-analysis of 38,000+ patients with acute and chronic HF showed that the presence of T2DM was an independent risk factor of increased all-cause mortality, cardiovascular mortality, and hospitalizations (8). Previous prevalence rates of T2DM among HF patients from clinical trials and registries have been estimated from selected in- and outpatient populations and ranged between 10% and 47% (6, 7). Only few studies have provided prevalence and trend estimates of T2DM among HF patients using population-based data (17-23); however, these studies included predominantly non-Hispanic white majority populations, therefore limiting the generalizability of results. Currently, no nationally representative data exists on the magnitude and temporal trends of T2DM among HF patients, nor on the sociodemographic and health characteristics of at-risk patients. Given the shared pathophysiology between HF and T2DM and the potential for synergistic treatment approaches, such information is essential for the development of targeted clinical guidance for the management of both coexisting conditions.

The primary objective of this study was to assess the prevalence and trends of T2DM (total, diagnosed, and undiagnosed) and prediabetes among U.S. community-dwelling HF patients using data from the National Health and Nutrition Examination Survey (NHANES) 2005-2006 to 2015-2016 cycles. Sociodemographic and health characteristics associated with T2DM, and prediabetes were examined.

Methods

Study Design and Population

The NHANES uses a multistage, stratified sampling design to recruit a nationally representative sample of the U.S. civilian, non-institutionalized population. The survey design and sampling methods have been described in detail elsewhere (274-276). The NHANES is an ongoing survey that collects publicly available data through in-home interviews and visits to a mobile examination center (MEC) in 2-year cycles. This study employed a secondary analysis of NHANES data using a cross-sectional design and used data obtained from survey cycles between 2005 and 2016.

The analytic sample included U.S. adults aged 20+ years with a self-reported physician diagnosis of HF who were randomly selected for the MEC fasting morning session based on NHANES sample design procedures (Appendix A.1). Participants selected for the MEC morning session were therefore representative of the entire sample (274-276). We only included participants who were randomly selected to attend the MEC morning session because of the availability of clinical parameters for fasting plasma glucose (FPG) and 2-hour plasma glucose (2hPG) after oral glucose tolerance test (OGTT). We did not observe differences in sociodemographic and health characteristics between participants aged 20+ years with HF who attended the MEC morning session and those who did not (Appendix A.2). The prevalence of HF among participants aged 20+ years who attended the MEC morning session was 2.6% (95% confidence interval [CI], 2.3-2.9%), which is comparable to prevalence estimates of HF in the

U.S. (2.2%) (3). Participants were excluded from the analyses if they 1) reported pregnancy (n = 2), 2) had missing data on self-reported physician diagnosis of diabetes (n = 0), 3) had incomplete data on diagnostic measures for diabetes unless they had a previous diagnosis of T2DM (n = 17), or if they 5) had type 1 diabetes mellitus (n = 4).

Data Collection

A standardized questionnaire was used to collect self-reported information, including sociodemographic and medical information. Participants' medication history was collected at in-home interviews (277). Sociodemographic information included age (≤ 64 or ≥ 65 years), gender (female or male), race/ethnicity (non-Hispanic white, non-Hispanic black, all Hispanic, or other), education level (< high school, high school graduate, or ≥ high school), and poverty income ratio (≤ 1.30, 1.31-3.50, or ≥ 3.51). Information on participants' medical history included history of heart disease (angina, coronary heart disease, myocardial infarction), hypertension, stroke, hospitalization(s) in the past 12 months (yes/no), and duration of HF (0-5 or 6+ years). Information on HF medication use included angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, loop diuretics, and nitrates and vasodilators. A self-reported physician diagnosis of HF was confirmed if participants answered affirmatively to the question: "Has a doctor or other health professional ever told you that you had congestive heart failure?" Further details about the data collection methods have been described elsewhere (277).

Clinical data in NHANES were collected using a standardized protocol at the MEC. Hemoglobin A1c (HbA1c) was measured in whole blood samples using instruments certified by the National Glycohemoglobin Standardization Program and standardized to the reference method used in the Diabetes Control and Complication Trials (278). Fasting plasma glucose concentrations were measured and OGTT results were conducted in all participants aged 12+ years, who were randomly selected for the morning fasting examination, following a 9-hour fast. The values of FPG and 2hPG were calibrated to make them comparable throughout survey cycles, as recommended by the National Center for Health Statistics (NCHS) (279).

Type 2 Diabetes Mellitus and Prediabetes

Diagnosed T2DM was defined by self-report of a previous physician diagnosis. Undiagnosed T2DM was defined by the absence of a previous physician diagnosis and the presence of ≥ 1 of 3 of the following American Diabetes Association diagnostic criteria: 1) 2hPG after OGTT ≥ 11.1 mmol/L (200 mg/dL), 2) HbA1c ≥ 48 mmol/mol (6.5%), 3) FPG ≥ 7.0 mmol/L (126 mg/dL). This definition was consistent with a previous study assessing prevalence estimates of undiagnosed T2DM in the U.S. general population (280). Total T2DM was defined as having diagnosed or undiagnosed T2DM. Prediabetes was defined by the absence of T2DM and the presence of ≥ 1 of 3 of the following American Diabetes Association diagnostic criteria: 1) 2hPG after OGTT of 7.8-11.0 mmol/L (140-199 mg/dL), 2) HbA1c of 42-47 mmol/mol (5.7-6.4%), 3) FPG of 6.1-6.9 mmol/L (100-125 mg/dL) (281). Individuals without a previous diagnosis of diabetes who did not meet these criteria were defined as not having diabetes. Individuals with type 1 diabetes were identified for exclusion if all of the following criteria were met: 1) diabetes diagnosis at age < 30 years, 2) current insulin use, and 3) starting insulin treatment within one year of diagnosis. This classification algorithm provided reliable estimates of the type 1 diabetes prevalence in the U.S. in a previous study (282).

Statistical Analysis

Survey analysis procedures with appropriately applied sample weights were used to account for the complex, multistage, probability sampling design and to produce nationally representative estimates of the U.S. civilian, non-institutionalized population. Participant characteristics were summarized using means and standard errors (SE) for continuous variables with normal distribution, median and interquartile ranges for continuous variables with non-normal distribution, and percentages for categorical variables. Differences in participant characteristics among the T2DM category groups were examined using the survey-weighted general linear models for continuous variables and Rao-Scott F adjusted chi-square tests for categorical variables.

The prevalence of total, diagnosed, and undiagnosed T2DM, and prediabetes in participants with HF from the NHANES 2005-2016 cycles was calculated and stratified by age, gender, race/ethnicity, education level, and poverty income ratio. Combining 6 NHANES cycles increased the reliability of the prevalence estimates by increasing the sample size. The results of the overall prevalence without stratification and age group strata were unstandardized, while the other stratified estimates were age-standardized using appropriate weights for age groups according to the 2000 Census data (20-44 years, weight, 0.5113; 45-64 years, weight, 0.3114; ≥65 years, weight, 0.1772). This was to enable comparisons within the stratification independent of age. Standard errors were calculated using the Taylor series method, and the corresponding 95% confidence limits were calculated using the arcsine transformation, as recommended by the NCHS (283, 284). The overall differences in prevalence by and within strata were examined by survey-weighted general linear models. Linear trends of the prevalence of T2DM and prediabetes were examined using each survey cycle as a continuous variable in logistic regressions. It was not necessary to impute missing values according to NHANES analytic guidelines since no variables had ≥ 11% of missing data (283, 284). Further, NHANES analytic guidelines consider a relative standard error (RSE) of ≤ 30% as statistically reliable, even when the sample size is small (283).

All statistical tests were 2-sided, and P-values of < 0.05 were considered statistically significant. P-values were adjusted by Bonferroni correction for multiple testing. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary NC).

Results

Characteristics of the Analytic Sample

A total of 527 U.S. adults with self-reported HF diagnosis were included in the analyses (n = 218 with diagnosed T2DM, n = 66 with undiagnosed T2DM, n = 175 with prediabetes, and n = 68 without diabetes). Among participants with HF and diagnosed T2DM, n = 134 were further classified as having had (pre-existing) T2DM prior to a HF diagnosis (data not shown). Descriptive characteristics of the analytic sample are presented in Table 3.1. On average, the analytic sample was older (mean age in years ± SE: 65.7 ± 0.8), non-Hispanic white (71.5%), and obese (31.4 ± 0.6 kg/m^2). The median length of HF duration since initial diagnosis was 7 years (IQR, 2-12 years). There were significant differences in sociodemographic and medical characteristics across participants with diagnosed, undiagnosed T2DM, prediabetes, and without diabetes. In comparison to participants without diabetes, the mean (± SE) age of individuals with T2DM or prediabetes was higher (diagnosed T2DM [mean age in years ± SE]: 67.2 ± 1.0, undiagnosed T2DM: 69.3 ± 1.4, prediabetes: 65.6 ± 1.4, no diabetes: 59.1 ± 2.6, respectively; $P = 0.006$). In addition, individuals with T2DM or prediabetes were more likely obese (body mass index [BMI]: 33.8 ± 0.7 kg/m^2, 31.3 ± 0.9 kg/m^2, 31.3 ± 0.9 kg/m^2, and 26.0 ± 0.6 kg/m^2, respectively; $P < 0.001$) and had higher systolic blood pressure (133.7 ± 1.6 mm Hg, 130.1 ± 4.3 mm Hg, 128.6 ± 2.2 mm Hg, and 122.3 ± 2.5 mm Hg, respectively; $P = 0.006$). Compared to participants without diabetes, those with T2DM or prediabetes were more likely to have chronic kidney disease (CKD; diagnosed T2DM: 45.2%, undiagnosed T2DM: 43.1%, prediabetes: 41.2%, no diabetes: 19.6%, respectively; P = 0.019), to have hypertension (88.0%, 72.3%, 79.9%, and 51.5%, respectively; P = 0.001), and to use angiotensin-converting enzyme inhibitors (40.1%, 37.9%, 43.4%, and 14.1%, respectively; P = 0.003), beta-blockers (63.7%, 71.5%, 56.8%, and 34.9%, respectively; P = 0.005), and loop diuretics (51.8%, 60.0%, 37.4%, and 18.2%, respectively; P < 0.001).

Prevalence of Type 2 Diabetes Mellitus and Prediabetes among Community-dwelling Heart Failure Patients

The prevalence of T2DM and prediabetes among community-dwelling HF patients during the 2005-2016 NHANES cycles is shown in Table 3.2. Prevalence estimates were 47.5% (95% CI, 42.3-52.7%) for total T2DM, 34.7% (95% CI, 29.2-40.3%) for diagnosed T2DM, 12.8% (95% CI, 9.2-16.9%) for undiagnosed T2DM, and 39.1% (95% CI, 33.6-44.9%) for prediabetes. In addition, prevalence estimates were 22.4% (95% CI, 17.4-27.8%) for pre-existing T2DM (data are not shown in the table).

Prevalence of Type 2 Diabetes Mellitus and Prediabetes among Community-dwelling Heart Failure Patients Stratified by Sociodemographic and Health Characteristics

We found the prevalence of total T2DM to be significantly different across race/ethnicity groups. Prevalence estimates of total T2DM were 27.1% (95% CI, 20.1-34.7%) in non-Hispanic whites, 33.0% (95% CI, 20.8-46.5%) in non-Hispanic blacks, 62.5% (95% CI, 44.1-79.2%) in Hispanics, and 11.3% (95% CI, 8.6-14.3%) in other race/ethnicity groups, respectively (P < 0.001). Compared to non-Hispanic white participants, the prevalence of total T2DM was significantly higher in Hispanics (P < 0.001) and lower in other race/ethnicity groups (P <

0.001). Similar trends were observed for the prevalence of diagnosed T2DM. Prevalence estimates of diagnosed T2DM were higher in Hispanics compared to non-Hispanic whites (52.1% [95% CI, 35.9-68.0%] and 20.1% [95% CI, 13.5-27.6%], respectively; $P < 0.001$). In non-Hispanic black participants in comparison to non-Hispanic white participants, the prevalence of total T2DM and diagnosed T2DM was 5.9% and 8.6% higher, respectively ($P = 0.439$ and $P = 0.237$, respectively). No statistically significant differences were observed for the prevalence of total T2DM, diagnosed T2DM, undiagnosed T2DM, and prediabetes across age, gender, education level, and poverty income ratio groups (poverty income ratio data are not shown).

We found prevalence estimates of undiagnosed T2DM among HF patients without reported hospitalization in the past 12 months to be 2-fold higher compared to HF patients with at least one hospitalization in the past 12 months (9.1% [95% CI, 4.7-14.7%] and 4.5% [95% CI, 2.3-7.3%], respectively; $P = 0.118$). In addition, the prevalence of total T2DM was significantly higher in HF patients who were obese compared to HF patients who were not obese ($BMI < 30kg/m^2$; 24.5% [95% CI, 14.7-35.9%] and 39.8% [95% CI, 30.8-49.1%], respectively; $P = 0.021$). Similar findings were observed for the prevalence of diagnosed T2DM across BMI categories (18.9% [95% CI, 9.8-30.1%] and 30.9% [95% CI, 22.3-40.3%]; $P = 0.078$). We further found HF patients with a history of stroke to have significantly higher prevalence estimates of total T2DM and diagnosed T2DM than those without a history of stroke (total T2DM: 75.7% [95% CI, 65.2-84.8%] and 31.8% [95% CI, 24.5-39.5%], respectively; $P < 0.001$; diagnosed T2DM: 69.4% [95% CI, 60.3-77.7%] and 24.4% [95% CI, 18.0-31.5%], respectively; $P < 0.001$). Similarly, HF patients with a history of comorbidities, including CKD ≥ stage 3, heart disease, and hypertension showed 10+% higher prevalence estimates of total T2DM than their counterparts (heart disease and hypertension data are not shown). No statistically significant differences were observed in the prevalence of total T2DM, diagnosed T2DM, undiagnosed T2DM, and prediabetes depending on the duration of HF.

Trends of Type 2 Diabetes Mellitus and Prediabetes among Community-dwelling Heart Failure Patients

Unweighted samples in individual NHANES cycles from 2005-2016 ranged from 70 to 98 participants (Figure 3.1). The prevalence of total T2DM was consistently high between 2005-2006 (43.8% [95% CI, 31.3-56.7%]) and 2015-2016 (45.3% [95% CI, 35.4-55.4%]; P = 0.373 for linear trends). This persistent trend was identified for diagnosed T2DM (2005-2006, 31.3% [95% CI, 14.8-50.7%]; 2015-2016, 34.1% [95% CI, 22.6-46.6%]; P = 0.887), undiagnosed T2DM (2005-2006, 12.5% [95% CI, 2.4-28.7%], RSE > 30%; 2015-2016, 11.2% [95% CI, 4.8-19.9%]), RSE > 30%; P = 0.402), and prediabetes (2005-2006, 39.0% [95% CI, 30.4-47.9%]; 2015-2016, 47.3% [95% CI, 33.6-61.3%]; P = 0.439).

Discussion

In this nationally representative sample of community-dwelling HF patients in the U.S., over 85% of patients showed signs of hyperglycemia: 47.5% had diagnosed or undiagnosed T2DM, and an additional 39.1% had prediabetes. Across racial/ethnic groups, Hispanic participants showed prevalence rates of over 50% for total and diagnosed T2DM; these prevalence estimates were more than twice as high as in non-Hispanic white participants. Additionally, 1 in 10 Hispanic participants with HF had undiagnosed T2DM. Trends of T2DM and prediabetes prevalence estimates among community-dwelling HF patients remained high through the NHANES 2005-2006 to 2015-2016 cycles.

Compared to the general U.S. population, the present study shows prevalence estimates of undiagnosed, total, and diagnosed T2DM that were 2-, 3-, and 4-fold higher in U.S. community-dwelling HF patients when using the same data source and T2DM diagnostic methodology (280). These elevated prevalence estimates of T2DM among community-dwelling HF patients are plausible on the basis of pathophysiological mechanisms underlying the coexistence of these two conditions. While T2DM has traditionally been viewed as a risk factor for HF development due to diabetic or ischemic cardiomyopathy induced by hyperglycemia, insulin resistance, and hyperinsulinemia, growing clinical and observational evidence suggest a bidirectional relationship of the two chronic conditions (285, 286). Heart failure-induced pathophysiological mechanisms, including sympathetic nervous system activation, neurohormonal abnormalities, elevated proinflammatory cytokines production, and metabolic alterations, likely contribute to insulin resistance and consequently result in heightened risk for new-onset T2DM (89). Only 22.4% of HF patients in our sample had pre-existing T2DM. Based on this finding, acknowledging the possibility of a reverse order of etiology carries importance for adequately addressing existing gaps in the care of at-risk patients.

While previously known predictors of T2DM among patients with HF, including elevated body mass index, diuretic therapy, and CKD (287), were confirmed by our study, we additionally discovered clinically useful information regarding sociodemographic and health characteristics associated with T2DM among HF patients. Knowledge of these characteristics will assist in better targeting at-risk HF patients in the U.S. in an attempt to reduce patient complications and healthcare costs. To our knowledge, this is the first study to find minority HF patients to be disproportionately burdened by T2DM. Participants of Hispanic origin showed prevalence estimates twice as high as non-Hispanic whites. In addition, prevalence estimates in non-

Hispanic blacks were over 5% higher in comparison to non-Hispanic whites. The heightened prevalence of T2DM among minorities in our nationally representative sample of U.S. community-dwelling adults likely explains the higher prevalence rates observed in our sample, when compared to previous studies in Europe and the U.S. that did not have adequate representation from minority populations in their samples. Previous diabetes prevalence estimates ranged between 11.7% and 31.7% (17-23). The heightened burden of T2DM we observed in Hispanic and non-Hispanic black HF patients in the U.S. carries importance for clinical practice, because, compared to their non-Hispanic white counterparts, Hispanics and non-Hispanic blacks experience greater barriers to diabetes self-management and inferior quality of diabetes care, including examinations of glycemia, blood pressure, and microvascular functions, leading to higher rates of diabetes complications and mortality (288, 289).

One in ten community-dwelling HF patients in our study had undiagnosed T2DM. The high prevalence of undiagnosed T2DM observed in our nationally representative sample of community-dwelling HF patients in the U.S. may be explained by several factors. First, current HF guidelines place little emphasis on T2DM screening for HF patients without previously diagnosed T2DM, and T2DM may therefore be missed (1, 36). Second, 34% of discharged HF patients receive no routine follow-up for HF outpatient care, and only 43% of them visit a cardiologist during the first three years after hospital discharge, resulting in a lack of opportunity to screen HF patients for T2DM (290). Our results showed that HF patients with at least 1 hospitalization in the past year showed much lower prevalence estimates of undiagnosed T2DM than those without hospitalization, suggesting that those who sought medical care may be more likely diagnosed. Given that previous studies show an increased risk of all-cause and cardiovascular mortality among HF patients with undiagnosed T2DM compared to those with diagnosed T2DM, HF guidelines should emphasize the importance of routinely screening HF patients for T2DM and consider multidisciplinary approaches to managing HF comorbidities.

Our study indicates that prevalence estimates of T2DM and prediabetes among U.S. community-dwelling HF patients remained at a high level between 2005 and 2016. These findings did not follow trends observed in the U.S. general population, which shows increasing trends of total and diagnosed diabetes between 1988 and 2012 (280). Among community-dwelling HF patients, the Olmsted study showed that prevalence estimates of diabetes increased from 13% during 1979-1984 to 25% during 1995-1999 (P = 0.03 for trends) (17), and the Framingham Heart Study showed increases of 23.2% during 1985-1994, 31.7% during 1995-2004, and 26.4% during 2005-2014 (results of trend analyses were not available) (18). The inconsistent results in prevalence trends over time may be attributed to the effect of racial and ethnic differences on survival of patients with HF, where the overall survival after the onset of HF has improved in the non-Hispanic white majority population while minorities still show a higher 5-year mortality rate (5, 49). Therefore, previous prevalence estimates of T2DM among HF patients in the non-Hispanic white majority population may demonstrate its increasing trends, whereas the current prevalence estimates of T2DM in our nationally representative sample of community-dwelling HF patients with adequate representation of minorities may show a more consistent trend of prevalence estimates over time.

This study has several limitations. Our study showed high standard errors with relatively wide confidence intervals due to the small raw sample size of eligible participants with HF due to the low overall prevalence of HF in the U.S. non-institutionalized population (2.6%, 95% CI 2.3-2.9%). However, most prevalence estimates had corresponding RSEs $\leq 30\%$, which indicate statistical reliability. Although more than 600 participants were excluded from our analyses due to not being selected for the morning MEC visit, the potential for selection bias should be considered minimal, because the MEC sessions were randomly assigned to participants according to NHANES sample design procedures. Appropriate sample weights for those, who attended the MEC morning session, were applied to our estimates in order to account for the complex, multistage, probability sampling design. Moreover, there was no difference in sociodemographic characteristics between participants aged 20+ years with HF who attended the MEC morning session and those who did not, which further supports that a potential selection bias was minimized. In addition, participants with undiagnosed T2DM were identified based on a single measurement of FPG, HbA1c, and 2hPG after OGTT following the NHANES protocol, which can potentially cause misclassification due to within-person variation and may consequently over- or under-estimate its prevalence (281). Repeated measurements are recommended to confirm T2DM and would provide a more accurate prevalence estimate of undiagnosed and total T2DM among community-dwelling HF patients. Despite these limitations, this study has high generalizability to community-dwelling HF patients in the U.S. civilian, non-institutionalized population, and provides valuable epidemiological information for healthcare providers.

In a nationally representative sample of U.S. community-dwelling HF patients, prevalence estimates of T2DM and prediabetes were persistently high over the past decade. Prevalence estimates of diagnosed or undiagnosed T2DM were more than twice as high in Hispanic than in non-Hispanic white patients. These substantially high prevalence estimates of T2DM and prediabetes among community-dwelling HF patients in the U.S. highlight the need to implement screening strategies and to develop targeted interventions to address T2DM, especially in Hispanic patients with HF.

Table 3.1. Sociodemographic and Medical Characteristics of U.S. Adults with Heart Failure across Type 2 Diabetes Mellitus Categories

	Total (n=527)	Diagnosed T2DM (n=218)	Undiagnosed T2DM (n=66)	Prediabetes (n=175)	No Diabetes (n=68)	P Value[a]
Sociodemographic Characteristics						
Age, mean (SE)	65.7 (0.8)	67.2 (1.0)	69.3 (1.4)	65.6 (1.4)	59.1 (2.6)	0.006
Female, No. (Weighted, %)	245 (49.4)	107 (52.8)	27 (42.8)	78 (48.3)	33 (49.8)	0.790
Race/Ethnicity, No. (Weighted, %)						
Non-Hispanic White	280 (71.5)	97 (63.5)	40 (81.2)	104 (76.4)	39 (68.7)	0.093
Non-Hispanic Black	128 (14.7)	64 (18.9)	14 (9.0)	35 (12.8)	15 (15.2)	
All Hispanic	93 (8.5)	49 (12.8)	10 (7.7)	25 (4.9)	9 (8.9)	
Other	26 (5.2)	8 (4.8)	2 (2.1)	11 (5.8)	5 (7.3)	
Education, No. (Weighted, %)[b]						
<High School	209 (33.4)	98 (38.7)	23 (27.6)	59 (29.4)	29 (36.7)	0.355
High School Graduate	124 (25.3)	48 (24.9)	21 (35.7)	40 (25.1)	15 (16.8)	
>High School	193 (41.3)	71 (36.4)	22 (36.7)	76 (45.5)	24 (46.5)	
Poverty Income Ratio, No. (Weighted, %)[b]						
≤1.30	204 (35.3)	88 (40.1)	25 (28.9)	63 (32.6)	28 (37.4)	0.805
1.31-3.50	191 (43.3)	79 (41.0)	21 (40.9)	68 (45.7)	23 (44.2)	
≥3.51	76 (21.4)	25 (18.9)	12 (30.2)	30 (21.7)	9 (18.4)	
Physical Examination and Laboratory Values						
Body Mass Index, mean (SE), kg/m^2	31.4 (0.6)	33.8 (0.7)	31.3 (0.9)	31.3 (0.9)	26.0 (0.6)	<0.001
Systolic Blood Pressure, mean (SE), mm Hg	129.7 (1.2)	133.7 (1.6)	130.1 (4.3)	128.6 (2.2)	122.3 (2.5)	0.006
Diastolic Blood Pressure, mean (SE), mm Hg	66.2 (0.7)	66.3 (1.0)	66.8 (2.0)	65.3 (1.2)	67.7 (1.2)	0.576
eGFR < 60 mL/min/1.73m^2, No. (Weighted, %)	207 (39.9)	93 (45.2)	26 (43.1)	74 (41.2)	14 (19.6)	0.019
Medical History, No. (Weighted, %)						
Angina	110 (22.3)	43 (21.6)	19 (24.6)	36 (24.4)	12 (15.8)	0.688
Coronary Heart Disease	188 (33.5)	77 (34.5)	27 (42.9)	61 (33.1)	23 (23.9)	0.374
Myocardial Infarction	228 (42.6)	91 (39.6)	27 (45.4)	82 (48.9)	28 (29.7)	0.196
Hypertension	426 (77.9)	187 (88.0)	53 (72.3)	142 (79.9)	44 (51.5)	0.001
Stroke	116 (22.0)	54 (26.5)	17 (23.5)	31 (16.8)	14 (24.1)	0.456
Duration of Heart Failure (Years)[b]						
0-5	223 (43.5)	84 (42.1)	25 (37.1)	84 (48.0)	30 (39.8)	0.549
6+	293 (56.5)	129 (57.9)	38 (62.9)	89 (52.0)	37 (60.2)	

Table 3.1. Sociodemographic and Medical Characteristics of U.S. Adults with Heart Failure across Type 2 Diabetes Mellitus Categories (Continue)

Hospitalization in the Past 12 Months[b]						
None	312 (63.0)	119 (63.3)	42 (63.6)	108 (62.6)	43 (62.8)	0.999
1+	214 (37.0)	98 (36.7)	24 (36.4)	67 (37.4)	25 (37.2)	
Medication Use, No. (Weighted, %)						
Angiotensin-converting Enzyme Inhibitors	195 (37.6)	91 (40.1)	21 (37.9)	70 (43.4)	13 (14.1)	0.003
Angiotensin II Receptor Blockers	78 (13.0)	37 (17.5)	8 (9.9)	27 (12.8)	6 (4.7)	0.077
Beta-blockers	314 (58.1)	140 (63.7)	41 (71.5)	105 (56.8)	28 (34.9)	0.005
Loop Diuretics	228 (42.7)	113 (51.8)	33 (60.0)	68 (37.4)	14 (18.2)	<0.001
Nitrates and Vasodilators	101 (18.4)	46 (17.9)	9 (9.9)	30 (22.7)	16 (14.8)	0.239

[a] P-value indicates significance of overall differences among T2DM category groups using survey-weighted general linear models for continuous variables and the Rao-Scott F adjusted chi-square tests for categorical variables.; [b] Raw counts did not sum to group total due to missing values; Abbreviations: eGFR, estimated glomerular filtration rate; SE, standard error; T2DM, type 2 diabetes mellitus.

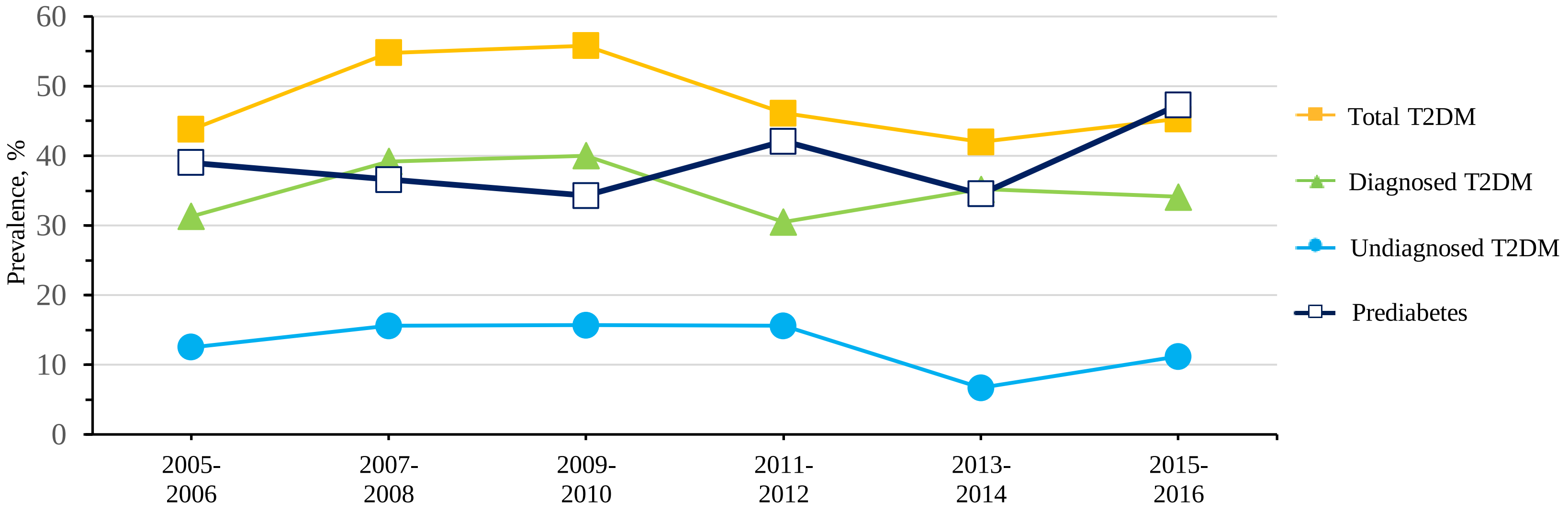
Table 3.2. Weighted Type 2 Diabetes Mellitus and Prediabetes Prevalence per 100 Adults with Heart Failure in the U.S., 2005-2016

		Total T2DM			Diagnosed T2DM		
	Total No.	No. of Cases[a]	Prevalence, % (95% CI)[b]	P Value[c]	No. of Cases[a]	Prevalence, % (95% CI)[b]	P Value[c]
Overall Prevalence	527	284	47.5 (42.3-52.7)		218	34.7 (29.2-40.3)	
Age Group (Years)							
≤ 64	203	102	42.1 (33.3-51.3)	0.124	83	33.0 (24.5-42.2)	0.608
65+	324	182	50.9 (44.7-57.0)		135	35.7 (29.4-42.3)	
Gender							
Female	245	134	32.5 (22.5-43.3)	0.746	107	27.6 (17.5-38.9)	0.753
Male	282	150	34.8 (24.6-45.8)		111	25.2 (15.9-35.7)	
Race/Ethnicity							
NH White (Ref.)	280	137	27.1 (20.1-34.7)	<0.001	97	20.1 (13.5-27.6)	<0.001
NH Black	128	78	33.0 (20.8-46.5)		64	28.7 (16.8-42.2)	
All Hispanic	93	59	62.5 (44.1-79.2)[d]		49	52.1 (35.9-68.0)[d]	
Others	26	10	11.3 (8.6-14.3)[d]		8	9.8 (6.6-13.5)[d]	
Education Level							
< HS (Ref.)	209	121	31.5 (22.0-41.9)	0.475	98	26.1 (16.7-36.9)	0.847
HS Graduate	124	69	39.4 (25.5-54.3)		48	28.8 (14.9-45.1)	
> HS	193	93	32.2 (20.5-45.0)		71	26.0 (15.7-37.9)	
Duration of HF (Years)							
0-5	223	109	34.3 (19.9-50.4)	0.851	84	27.2 (12.8-44.6)[e]	0.610
6+	293	167	36.1 (22.1-51.4)		129	22.3 (12.9-33.3)	
Hospitalization							
None	312	161	36.7 (26.1-48.0)	0.308	119	27.6 (18.9-37.3)	0.656
1+	214	122	29.4 (20.1-39.6)		98	24.9 (15.8-35.2)	
Body Mass Index							
Not Obese	247	103	24.5 (14.7-35.9)	0.021	77	18.9 (9.8-30.1)	0.078
Obese	255	161	39.8 (30.8-49.1)		131	30.9 (22.3-40.3)	
CKD ≥ Stage 3							
No	296	143	31.7 (24.2-39.8)	0.317	104	24.2 (17.6-31.4)	0.275
Yes	207	119	44.1 (22.0-67.5)		93	37.4 (16.4-61.2)[e]	
Stroke							
No	409	211	31.8 (24.5-39.5)	<0.001	164	24.4 (18.0-31.5)	<0.001
Yes	116	71	75.7 (65.2-84.8)		54	69.4 (60.3-77.7)	

Table 3.2. Weighted Type 2 Diabetes Mellitus and Prediabetes Prevalence per 100 Adults with Heart Failure in the U.S., 2005-2016 (Continue)

	Undiagnosed T2DM			Prediabetes		
	No. of Cases[a]	Prevalence, % (95% CI)[b]	P Value[c]	No. of Cases[a]	Prevalence, % (95% CI)[b]	P Value[c]
Overall Prevalence	66	12.8 (9.2-16.9)		175	39.1 (33.6-44.9)	
Age Group (Years)						
≤ 64	19	9.1 (4.7-14.8)	0.105	64	38.7 (29.0-48.8)	0.899
65+	47	15.2 (10.2-20.9)		111	39.5 (32.5-46.6)	
Gender						
Female	27	4.9 (2.5-8.0)	0.171	78	42.0 (24.6-60.5)	0.927
Male	39	9.7 (4.6-16.3)[e]		97	41.0 (28.5-54.1)	
Race/Ethnicity						
NH White (Ref.)	40	7.0 (4.1-10.7)	0.089	104	46.3 (29.0-64.1)	0.039
NH Black	14	4.4 (1.9-7.7)[e]		35	39.9 (22.1-59.2)	
All Hispanic	10	10.4 (3.0-21.6)[e]		25	19.2 (7.5-34.7)[d,e]	
Others	2	1.5 (0.0-5.2)[d,e]		11	53.9 (25.4-81.1)	
Education Level						
< HS (Ref.)	23	5.4 (3.0-8.4)	0.264	59	38.9 (22.5-56.7)	0.762
HS Graduate	21	10.6 (5.7-16.9)		40	39.5 (22.0-58.4)	
> HS	22	6.2 (1.8-12.9)[e]		76	44.0 (27.6-61.0)	
Duration of HF (Years)						
0-5	25	7.2 (3.7-11.7)	0.359	84	41.0 (23.2-60.1)	0.570
6+	38	13.8 (3.3-29.9)[e]		89	48.9 (28.3-69.7)	
Hospitalization						
None	42	9.1 (4.7-14.7)	0.118	108	42.7 (30.6-55.1)	0.746
1+	24	4.5 (2.3-7.3)		67	39.3 (22.2-57.9)	
Body Mass Index						
Not Obese	21	5.6 (2.9-9.1)	0.343	95	38.7 (19.4-60.1)	0.611
Obese	30	8.8 (4.0-15.3)[e]		76	45.1 (33.2-57.3)	
CKD ≥ Stage 3						
No	39	7.6 (4.5-11.4)	0.827	100	40.9 (30.0-52.2)	0.900
Yes	26	6.7 (1.5-15.3)[e]		74	42.6 (20.0-66.9)	
Stroke						
No	47	7.4 (4.2-11.3)	0.720	144	42.8 (32.3-53.6)	<0.001
Yes	17	6.3 (2.6-11.5)[e]		31	17.4 (8.8-28.3)	

Obese was defined as body mass index ≥ 30 kg/m^2. CKD ≥ Stage 3 was defined as estimated glomerular filtration rate < 60 mL/min/1.73m^2.; [a] Unweighted total number of cases. Raw Counts did not sum to group total due to missing values.; [b] Overall and age group results are non-age-standardized. Gender, race/ethnicity, and poverty income ratio groups are age-standardized to the 2000 Census data.; [c] P-value indicates significance of overall differences in prevalence by strata.; [d] The prevalence is significantly different compared to the reference groups.; [e] Relative standard error > 30%.; Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HF, heart failure; HS, high school; NH, non-Hispanic; Ref, reference; T2DM, type 2 diabetes mellitus.



	2005-2006	2007-2008	2009-2010	2011-2012	2013-2014	2015-2016	P Value for Linear Trends
Total T2DM	43.8 (31.3-56.7)	54.8 (43.2-66.1)	55.8 (38.7-72.1)	46.1 (31.9-60.7)	42.0 (34.5-49.6)	45.3 (35.4-55.4)	0.373
Diagnosed T2DM	31.3 (14.8-50.7)	39.2 (31.0-47.8)	40.0 (23.3-58.1)	30.5 (18.3-44.2)	35.2 (26.7-44.2)	34.1 (22.6-46.6)	0.887
Undiagnosed T2DM	12.5 (2.4-28.7)[a]	15.6 (7.1-26.5)[a]	15.7 (8.5-24.6)	15.6 (6.8-27.3)[a]	6.7 (3.3-11.3)	11.2 (4.8-19.9)[a]	0.402
Prediabetes	39.0 (30.4-47.9)	36.6 (27.0-46.8)	34.3 (20.1-50.1)	42.1 (27.7-57.3)	34.5 (21.3-49.1)	47.3 (33.6-61.3)	0.439

Figure 3.1. Prevalence Trends in Type 2 Diabetes Mellitus and Prediabetes among Heart Failure Patients – Trend Estimates of Type 2 Diabetes Mellitus (Total, Diagnosed, and Undiagnosed) and Prediabetes per 100 U.S. Adults with Heart Failure, 2005-2016 (P > 0.050 for the Linear Trends). Superscript of "a" indicates relative standard error > 30%. Abbreviation: T2DM, type 2 diabetes mellitus.

CHAPTER 4

COMPARISON OF DIAGNOSTIC METHODS FOR DIABETES IN PATIENTS WITH HEART FAILURE: A NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY ANALYSIS [3]

---

[3] Ishikawa Y, Laing EM, Anderson AK, Zhang D, Kindler JM, Trivedi-Kapoor R, Sattler ELP. To be submitted.

Abstract

Objective

The use of hemoglobin A1c (HbA1c) to diagnose diabetes among cardiovascular disease patients has shown low sensitivity. The objective of the study was to compare the diagnostic performance of HbA1c, fasting plasma glucose (FPG), and two-hour plasma glucose (2hPG) among heart failure (HF) patients.

Research Design and Methods

We included 237 HF patients aged 20+ years without history of diabetes, using data from the National Health and Nutrition Examination Survey 2005-2016. Diagnostic diabetes criteria were based on the American Diabetes Association guidelines: (1) HbA1c ≥6.5%, (2) FPG ≥126 mg/dL, and (3) 2hPG ≥200 mg/dL. The sensitivity, specificity, and Receiver Operating Characteristic (ROC) curves for HbA1c and FPG were examined against 2hPG as the reference method.

Results

Included participants had a mean age of 65±1 (SE) years, 45.5% were female, and 12.5% were non-Hispanic black. Among included participants, 50 patients (20.5%) met at least 1 of 3 clinical criteria for diabetes. 2hPG alone identified 70.5% of patients, whereas HbA1c alone identified only 27.0% of patients. Sensitivity and specificity using a HbA1c cutoff at ≥6.5% were 24.4% and 97.6%, respectively. The Youden's J statistic for HbA1c was maximized at 6.1%. The area under the ROC curve of HbA1c against 2hPG was significantly lower compared to FPG (0.79, 95% CI 0.70-0.88; 0.89, 95% CI 0.84-0.94, respectively; p=0.04).

Conclusions

Blood glucose criteria are preferred over HbA1c when diagnosing diabetes among patients with HF. The recommended HbA1c cutoff should be lowered to 6.1% for HF patients when FPG or 2hPG cannot be completed.

Introduction

The progressive nature of heart failure (HF) pathophysiology, including the development of neurohormonal, metabolic, and immunological abnormalities, place HF patients at high risk for developing new-onset type 2 diabetes (7). Coexisting HF and diabetes, in comparison to HF alone, are associated with higher risks of all-cause and cardiovascular mortality and heart failure-related hospitalizations (8). The risk of complications and mortality is particularly problematic for HF patients with coexisting undiagnosed diabetes, which affects up to 22% of HF patients (81). In a retrospective cohort study, the mortality risk of HF patients with undiagnosed diabetes was similar to the risk of HF patients with diagnosed diabetes although individuals with HF and undiagnosed diabetes demonstrated a lower overall cardiovascular risk profile, as shown by a lower prevalence of hypertension, dyslipidemia, peripheral vascular disease, and previous myocardial infarction (291). These findings suggest the need to routinely screen HF patients for the presence of type 2 diabetes which appears to be critical to improving HF prognoses.

The American Diabetes Association (ADA) currently recommends a diagnosis of diabetes to be based on one or more of the following measures: 1) fasting plasma glucose (FPG) level ≥ 126 mg/dL, 2) two-hour plasma glucose (2hPG) after oral glucose tolerance test (OGTT) ≥ 200 mg/dL, 3) hemoglobin A1c (HbA1c) value ≥ 6.5%, and 4) patients with classic symptoms of hyperglycemia, hyperglycemic crisis, or a random plasma glucose ≥ 200 mg/dL (292). The ADA states that these measures are equally appropriate for diagnostic screening (292). However, growing evidence in populations with cardiovascular diseases suggests that there is limited accordance among HbA1c, FPG, and 2hPG as diagnostic measures for diabetes. The European Action on Secondary Prevention through Intervention to Reduce Events (EUROASPIRE) IV study reported that, among 4,004 coronary artery disease patients with no history of diabetes, 1,158 patients were newly diagnosed with diabetes: FPG alone identified 75%, 2hPG identified 40%, and HbA1c alone identified 17% of cases (24). Only 7% of cases were identified by all three methods (24). Observational studies in coronary artery disease and acute coronary syndrome patients with no history of diabetes showed that, using FPG ≥ 126mg/dL and/or 2hPG ≥ 200 mg/dL as reference for diabetes diagnosis, the recommended HbA1c cutoff point for a diagnosis of diabetes (≥ 6.5%) had low sensitivity at 16-29% (25-27). In addition, the area under the curve (AUC) of the Receiver Operating Characteristic (ROC) curve of HbA1c for the identification of patients with diabetes ranged from 0.48 to 0.73, which indicated insufficient accuracy for diagnosing diabetes (25-27). Therefore, using HbA1c as diagnostic criterion alone likely falls short of correctly diagnosing new-onset type 2 diabetes in patients with cardiovascular diseases.

Previous evidence on the potentially suboptimal performance of HbA1c among cardiovascular disease patients stems exclusively from populations with coronary artery disease and acute coronary syndrome (25-27). Compared to patients with coronary artery disease and acute coronary syndrome, however, patients with HF are more vulnerable to anemia due to impaired erythropoiesis in bone marrow (293), which is a known mechanism impairing the formation of hemoglobin and HbA1c. Consequently, HbA1c measurements are less reliable among patients with anemia (294-298). Given that anemia is present in about 30% of stable and about 50% of hospitalized HF patients and that it is more common among HF patients with diabetes (293), an investigation into the appropriateness of diabetes diagnostic methods in this population is warranted.

This study aimed to compare the performance of current diagnostic methods for type 2 diabetes among HF patients. A better understanding of the clinical performance of diabetes diagnostic measures among HF patients will improve existing clinical guidance aimed at preventing complications in medically complex HF patients.

Research Design and Methods

Study Design and Population

This cross-sectional study included data from National Health and Nutrition Examination Survey (NHANES) cycles between 2005 and 2016. The NHANES is an ongoing survey conducted since 1999 by the National Center for Health Statistics (NCHS) of the Centers for Disease Control Prevention, and uses a multistage, stratified sampling design to represent a nationally representative sample of the civilian, non-institutionalized population in the United States (274-276). The NHANES study protocols were approved by the research ethics boards of the NCHS, and all participants provided written informed consent before the data collection.

The analytic sample included participants aged 20+ years with a self-reported physician-diagnosis of HF. Participants were excluded if they 1) did not attend the Mobile Examination Center (MEC) morning session which is required for obtaining the fasting clinical parameters used in our analyses, 2) reported a self-reported physician-diagnosis of diabetes or diabetes medication use, because individuals with diabetes were excluded from OGTT data collection according to NHANES procedures (283), which has been described in previous studies (25-27), 3) had incomplete data on HbA1c, FPG, and 2hPG after OGTT, or 4) if they were pregnant. Any potential for selection bias was minimized by applying appropriate sample weights in our analysis in order to account for the complex, multistage, probability sampling design (283).

Data Collection

The NHANES uses a standardized questionnaire which is implemented at in-home interviews to collect sociodemographic and medical information. Sociodemographic information included in our study were age, gender, race/ethnicity, education level, and poverty income ratio. Information on participants' medical history included angina, coronary heart disease, myocardial infarction, hypertension, stroke, duration of HF, need for dialysis, and hospitalization(s) in the past 12 months. Medication history information was collected at in-home interviews by brown bag medication review. In the present analyses, information on HF medication use included angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARBs), beta-blockers, loop diuretics, and hydroxymethylglutaryl (HMG) coenzyme A reductase inhibitors ("statins"). A self-reported physician diagnosis of HF was confirmed if participants answered "yes" to the question: *"Has a doctor or other health professional ever told you that you had congestive heart failure?"* Further details about the data collection methods have been described elsewhere (277).

Anthropometric and clinical data were collected according to a standardized protocol at the MEC visits. Anemia was defined as hemoglobin levels < 13 g/dL for men and < 12 g/dL for women (299). Estimated glomerular filtration rates (eGFR) were calculated using the Modification of Diet in Renal Disease Study equation (300), and eGFR < 60 mL/min/1.73m^2 were categorized as chronic kidney disease (CKD). Assessment of HbA1c was performed using instruments certified by the National Glycohemoglobin Standardization Program and standardized to the reference method used in the Diabetes Control and Complication Trials. The calibration of HbA1c was not conducted in this study, as recommended by NCHS (279). Assessments of FPG and 2hPG were performed in all included participants following a 9-hour fast. After the initial blood specimen collection, participants were asked to drink a calibrated dose (75 grams) of glucose and plasma glucose was measured 2 hours (±15 minutes) later. The calibrations for FPG and 2hPG were performed using suggested regression equations by NCHS since instruments and methods used for these assessments have changed over different survey cycles (301).

Diagnostic Criteria for Diabetes

Diagnostic criteria for diabetes were based on the ADA guideline (292), which defines a diagnosis of diabetes according to the following values: 1) HbA1c $\geq$ 6.5%, 2) FPG $\geq$ 126 mg/dL, and/or 3) 2hPG $\geq$ 200 mg/dL. Although the ADA guidelines recommend at least 2 abnormal test results, either from the same blood sample or from two separate blood samples, to confirm a diabetes diagnosis (292), a single measurement of HbA1c, FPG, and 2hPG following NHANES procedures is considered sufficient for the screening-yield comparison with these methods, as shown in previous studies (24-26, 302).

Statistical Analysis

Survey analysis procedures with appropriate sample weights were used to account for the complex, multistage, probability sampling design (e.g., oversampling, nonresponse, and noncoverage). Participant characteristics were summarized using means and standard errors (SE) for continuous variables with normal distribution, medians and interquartile ranges (IQR) for continuous variables with non-normal distribution, and percentages for categorical variables. The ability to diagnose diabetes with each of the 3 diagnostic methods at their respective cutoff points was measured by calculating sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV), respectively. The Youden’s J statistic for optimal diagnostic cutoff points were calculated for HbA1c and FPG using the following equation: sensitivity + specificity – 1 (303). Cohen’s kappa coefficient was calculated to assess the interrater reliability between the respective diagnostic methods using the Jackknife variance estimation method. Receiver Operating Characteristic (ROC) curves were examined for the diagnosis of diabetes based on HbA1c against FPG (≥ 126 mg/dL) and HbA1c and FPG against 2hPG (≥ 200 mg/dL), respectively. The equivalence test for the AUCs of ROCs between HbA1c and FPG against 2hPG was performed using the Chi-square tests (304).

All statistical tests were 2-sided, and P values < 0.05 were considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R statistical software version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 1,154 NHANES participants met age and HF inclusion criteria. After excluding participants who did not attend the MEC morning session (n = 604), did not report a history of physician-diagnosis of diabetes or diabetes medication use (n = 230), had incomplete data on diagnostic measures for diabetes (n = 83), or were pregnant (n = 0), n = 237 participants were included into the analyses (Appendix B.1). The prevalence of HF among participants aged 20+ years who attended the MEC morning session was 2.6% (95% confidence interval [CI], 2.2-2.9%) which is comparable to previous prevalence estimates of HF in the U.S. population (3). Included and excluded participants did not show significant differences in most sociodemographic and medical characteristics; however, included participants were more likely non-Hispanic white (77.1% vs. 67.7%, respectively; p = 0.007), and more likely to report a history of coronary heart disease (33.0% vs. 41.1%, respectively; p = 0.038) and hypertension (68.7% vs. 80.9%, respectively; p = 0.001) (Appendix B.2).

Sociodemographic and medical characteristics of the study participants are summarized in Table 4.1. On average, participants were older (mean age ± SE: 65.0 ± 1.1 years), and predominantly male (54.5%), non-Hispanic white (74.6%), and obese (44.4%). A large proportion of participants had an education level greater than high school diploma (46.1%) and a poverty income ratio between 1.31-3.50 (46.0%). Most individuals reported a history of hypertension (70.1%), 6+ years since the first physician diagnosis of HF (55.5%), and beta-blockers use (52.2%). Fifty-two patients (21.0%) had anemia, and 93 patients (39.2%) had CKD. Seventy-nine (36.0%) and 30 (9.9%) patients took ACEi and ARBs, respectively. Median levels of FPG, 2hPG, and HbA1c were 104.3 (IQR: 95.6-115.8) mg/dL, 135.7 (IQR: 95.1-169.3) mg/dL, and 5.6 (IQR: 5.3-5.9) %, respectively.

Fifty patients (20.5%) met at least one of three clinical criteria for diabetes. The proportions of participants who met at least 1 of 3 clinical criteria for diabetes and their overlap are shown in Figure 4.1. Of the 50 participants diagnosed with diabetes, 27.0% were identified by HbA1c alone, 49.8% by FPG alone, 70.5% by 2hPG alone, 64.5% by FPG and/or HbA1c, and 90.1% by FPG and/or 2hPG. The proportion of individuals being diagnosed with diabetes by all 3 methods was 12.3%.

Cohen’s kappa coefficients for diabetes diagnosis using the ADA recommended cutoff point of FPG, 2hPG, and HbA1c are shown in Table 4.2. The interrater reliability between HbA1c and blood glucose criteria indicated fair agreement, where Cohen’s kappa coefficients of HbA1c to FPG and 2hPG were 0.27 and 0.30, respectively. In contrast, the interrater reliability between FPG and 2hPG indicated moderate agreement, showing Cohen’s kappa coefficient of 0.43.

The ROC curves assessing performances of HbA1c and FPG in diagnosing diabetes are presented in Figure 4.2. The ROC curve assessing the performance of HbA1c in diagnosing diabetes, defined by FPG $\geq$ 126mg/dL, indicated fair performance, as shown by an AUC of the ROC curve of 0.74 (95% CI, 0.63-0.85) (Figure 4.2-A). The ADA recommended HbA1c cutoff point for the diagnosis of diabetes (≥ 6.5%) had low sensitivity at 24.7% and high specificity at 96.7%, with a PPV of 45.5% and an NPV of 91.9%. The Youden's J statistic for HbA1c was maximized at 5.9% (62.5% sensitivity and 66.8% specificity). Similar trends were identified for the performance of HbA1c in diagnosing diabetes, defined by 2hPG ≥ 200 mg/dL, as shown by an AUC of the ROC curve of 0.79 (95% CI, 0.70-0.88). Sensitivity and specificity using the HbA1c cutoff at 6.5% were 24.4% and 97.6%, respectively (Figure 4.2-B). The Youden's J statistic for HbA1c was maximized at 6.1% (57.4% sensitivity and 86.9% specificity). In contrast, the performance of FPG in diagnosing diabetes, defined by 2hPG ≥ 200 mg/dL, was excellent, as shown by an AUC of the ROC curve of 0.89 (95% CI, 0.84-0.94). Sensitivity and specificity using the recommended FPG cutoff point (≥ 126 mg/dL) were 42.7% and 95.3%, respectively (Figure 4.2-C). The Youden's J statistic for FPG was maximized at 110 mg/dL (93.1% sensitivity and 75.2% specificity). The AUC of the ROC curves for the performance of FPG in diagnosing diabetes, defined by 2hPG ≥ 200 mg/dL, was significantly higher than the performance of HbA1c (p = 0.04).

Conclusions

Among this nationally representative sample of community-dwelling HF patients with no known history of diabetes, 20.5% of participants met at least one of the ADA diagnostic criteria for diabetes. Among these participants, the overlap in diabetes case detection among HbA1c, FPG, and 2hPG was very small. Hemoglobin A1c alone identified the smallest number of the cases (27.0%), whereas 2hPG alone detected the largest number of cases (70.5%). The overall performance of HbA1c to identify diabetes, using 2hPG as the reference method, was suboptimal and significantly lower than the performance of FPG. Consequently, screening for diabetes with the currently recommended HbA1c cutoff point at 6.5% would have left 76% of patients undiagnosed.

The present study suggests that use of HbA1c alone at the currently recommended cutoff point of < 6.5% is insufficient in adequately diagnosing diabetes among HF patients. In our sample, HbA1c identified only about one-quarter of individuals with diabetes, as measured by 2hPG. These findings are consistent with a small cross-sectional study among 56 patients with chronic HF in which 14 patients were newly diagnosed with diabetes (305). A total of 11 patients (76%) were identified by 2hPG alone, 2 patients (14%) by FPG and 2hPG, and 1 patient (7%) by FPG alone (305). In this study, none of the participants with newly diagnosed diabetes was identified by HbA1c. In addition, low sensitivity of HbA1c in diagnosing diabetes compared to FPG and 2hPG, as found by our study, has previously been reported among patients with coronary artery disease or acute coronary syndrome in Europe (25-27). These findings stand in contrast to evidence supporting HbA1c as adequate diagnostic method in the diagnosis of diabetes among individuals without cardiovascular diseases. A meta-analysis in individuals without established cardiovascular diseases showed that the AUC of ROC curves of HbA1c in diagnosing diabetes, as confirmed by 2hPG, indicated excellent performance (AUC 0.89; 95% CI 0.86-0.91) while HbA1c at 6.5% had a sensitivity of 0.68 and specificity of 0.96 (306). Furthermore, the AUC of HbA1c was not significantly different to the AUC of FPG in patients without cardiovascular diseases. The ADA clinical guidelines consider HbA1c, FPG, and 2hPG as equally appropriate measures when screening patients for diabetes; however, it is likely that when cardiovascular patients are screened for diabetes by using HbA1c alone, a large proportion of cases are missed.

The mechanisms underlying the low performance of HbA1c in identifying diabetes among cardiovascular patients may be explained by impaired formation of erythropoiesis in bone marrow due to anemia. Anemia is a common comorbidity in cardiovascular disease patients (293). Previous studies reported that up to 43% of coronary artery disease patients (307), 30 % of stable HF patients, and 50% of hospitalized HF patients had anemia (293). In our study, one in five community-dwelling HF patients had coexisting anemia. The pathophysiology of anemia among HF patients involves impaired erythropoiesis in bone marrow resulting from several mechanisms (293). These proposed mechanisms are supported by a meta-analysis of over 3,000 stable HF patients that confirmed HF patients with coexisting anemia to have a lower observed/predicted erythropoietin ratio than those without anemia (308). Abnormal neurohormonal activation as compensatory mechanism of cardiac dysfunction increases proinflammatory cytokine production (13), and chronic inflammation which contribute to impaired erythropoiesis (309). In addition, impaired erythropoiesis among HF patients is caused by absolute iron-deficiency, caused by a reduction of total body iron store levels associated with anorexia, intestinal edema-induced iron malabsorption, iron maldistribution by hepcidin-induced downregulation of iron transporters, and functional iron-deficiency due to inflammatory cytokine-induced upregulation of hepatic hepcidin production (293). Furthermore, erythropoiesis may be suppressed by HF pharmacotherapy, including ACEi and ARBs, which inhibit angiotensin II formation, which is a trigger of erythropoietin synthesis, and an increase N-acetyl-seryl-aspartyl-lysyl-proline, a strong inhibitor of erythropoiesis (293). Ultimately, the significant reduction in plasma erythropoietin levels, caused by the aforementioned mechanisms, may lead to the selective destruction of newly formed erythrocytes via neocytolysis which ultimately impacts the formation of HbA1c (294). Consequently, measured HbA1c levels may appear to be artificially reduced without affecting blood glucose levels. Given the high frequency of anemia among HF patients and the findings of our study, it might be advisable for clinicians to prioritize FPG or 2hPG over HbA1c measurements when screening for diabetes if an OGTT cannot be performed.

Although the low sensitivity of HbA1c measurements seems problematic for adequately identifying diabetes among HF patients, it may be the only widespread practically feasible option within the HF population. A previous clinical study found that 31% of 331 eligible patients with HF declined to undergo overnight fasting or an OGTT (82). The authors discussed that the patient burden of fasting may not be possible for older and physically impaired HF patients with comorbidities. The present study demonstrated that the Youden's J statistic for HbA1c was maximized at 6.1% with 57.4% sensitivity and 86.9% specificity for a diabetes diagnosis in reference to 2hPG. Considering the difficulties faced with collecting fasting patient information, a HbA1c cutoff point at 6.1% may be considered as diagnostic diabetes criterion for HF patients. Further evidence on the prognostic impact and cost-effectiveness regarding the suggested tailored cutoff of HbA1c is warranted.

There are several potential limitations in this study. Over 900 participants aged 20+ years with HF were excluded from our analyses, which may introduce an impression of selection bias. However, 65% of individuals were excluded as a result of not being randomly selected for the MEC morning session during which clinical parameters required for our study were collected. More information regarding the NHANES sampling procedures and the representativeness of the sample invited to the MEC morning session were described elsewhere (274-276). We used appropriate survey weights to account for the complex, multistage, probability sampling design. Furthermore, the absence of detailed information on HF characteristics in NHANES datasets, including HF subtypes and severity of symptoms, may affect interpretation of our results for clinical sub-populations. Nevertheless, our study provided clinically important information regarding diagnostic measures of diabetes among HF patients using a nationally representative sample of community-dwelling HF patients in the U.S.

In summary, the accordance among HbA1c, FPG, and 2hPG as diagnostic measures for diabetes is limited among HF patients. Our findings suggest that blood glucose criteria may be preferred over HbA1c to screen for diabetes among HF patients without a history of diabetes. Finally, a tailored HbA1c cutoff point at 6.1% as criterion for diabetes diagnosis should be considered for HF patients when FPG and 2hPG cannot be assessed.

Table 4.1. Sociodemographic and Medical Characteristics of U.S. Adults with Heart Failure

	Total (n = 237)
Sociodemographic Characteristics	
Age, mean (SE)	65.0 (1.1)
Female, %	45.5
Race/Ethnicity, %	
Non-Hispanic White	74.6
Non-Hispanic Black	12.5
All Hispanic	6.6
Other	6.3
Education, %	
Less than High School	31.3
High School Graduate	22.6
More than High School	46.1
Poverty Income Ratio, %	
≤ 1.30	33.5
1.31-3.50	46.0
≥ 3.51	20.5
Physical Examination and Laboratory Values	
BMI Classification, %	
≤ Normal Weight (BMI ≤ 24.9 kg/m^2)	26.4
Overweight (BMI 25.0-29.9 kg/m^2)	29.2
≥ Obesity (BMI ≥ 30 kg/m^2)	44.4
Systolic Blood Pressure, Mean (SE), mm Hg	126.7 (1.7)
Diastolic Blood Pressure, Mean (SE), mm Hg	66.0 (0.9)
Fasting Plasma Glucose, Median (IQR), mg/dL	104.3 (95.6-115.8)
2-Hours Plasma Glucose, Median (IQR), mg/dL	135.7 (95.1-169.3)
Hemoglobin A1c, Median (IQR), %	5.6 (5.3-5.9)
Medical History, %	
Newly Diagnosed Diabetes	20.5
Anemia	21.0
Angina	24.5
Coronary Heart Disease	32.7
Chronic Kidney Disease	39.2
Dialysis in the Past 12 Months	1.6
Myocardial Infarction	46.6
Hypertension	70.1
Stroke	18.8
Duration of Heart Failure (Years)	
0-5	44.5
6+	55.5
Hospitalization in the Past 12 Months	
None	62.6
Once	20.5
Twice+	16.9
Medication History, %	
Angiotensin-Converting Enzyme Inhibitors	36.0
Angiotensin II Receptor Blockers	9.9
Beta-blockers	52.2
Loop Diuretics	38.4
Statin	49.5

Abbreviations: BMI, body mass index; IQR, interquartile range; SE, standard error.

Table 4.2. Cohen's Kappa Coefficients for Diabetes Diagnosis among Hemoglobin A1c, Fasting Plasma Glucose, and 2-hour Plasma Glucose

	HbA1c	FPG	2hPG
HbA1c ≥ 6.5%	-	0.27	0.30
FPG ≥ 126 mg/dL	0.27	-	0.43
2hPG ≥ 200 mg/dL	0.30	0.43	-

Abbreviations: 2hPG, 2-hour plasma glucose; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c.

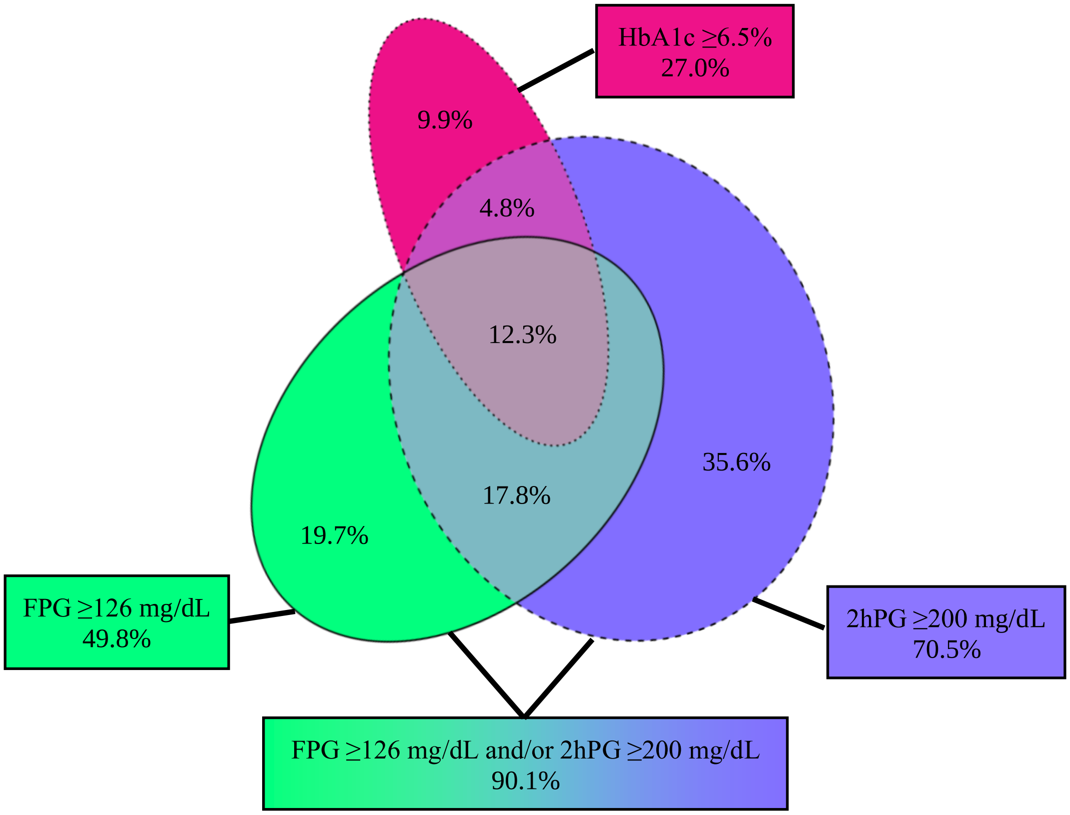
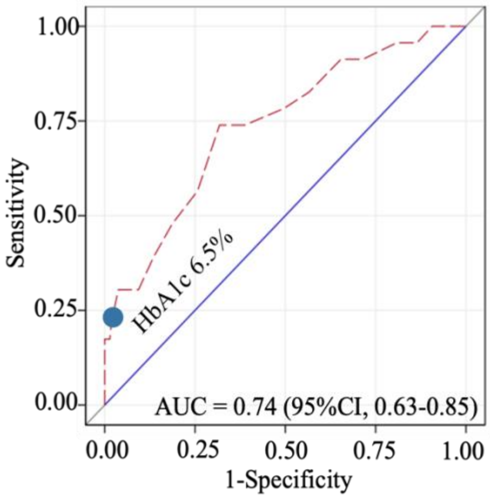


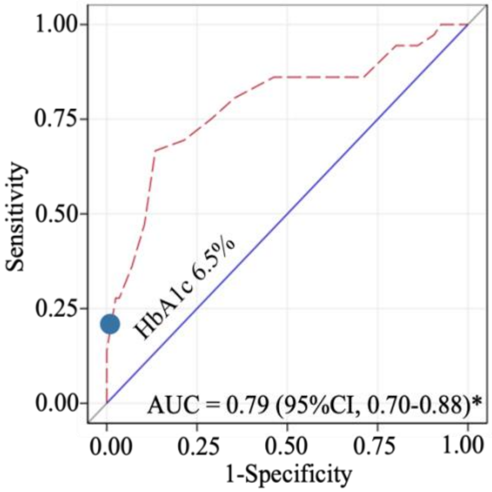
Figure 4.1. Proportions of Participants with Heart Failure and Newly Diagnosed Diabetes as Identified by Hemoglobin A1c, Fasting Plasma Glucose, and 2-hour Plasma Glucose and Their Overlap. 2hPG = 2-hour plasma glucose; FPG = fasting plasma glucose; HbA1c = hemoglobin A1c.

A. ROC curve of HbA1c in diagnosing diabetes (FPG ≥ 126 mg/dL)



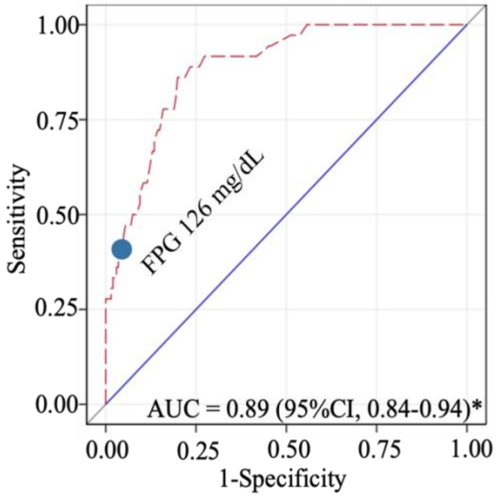
HbA1c, %	SEN, %	SPE, %	J Value	PPV, %	NPV, %
5.5	83.3	34.7	0.18	12.6	94.8
5.6	68.2	42.3	0.10	11.8	92.1
5.7	63.9	47.2	0.11	12.1	92.0
5.8	62.5	60.0	0.23	15.1	93.4
5.9	62.5	66.8	0.29	17.6	94.0
6.0	42.2	75.0	0.17	16.1	92.0
6.1	35.7	82.4	0.18	18.7	91.9
6.2	29.2	86.8	0.16	20.0	91.5
6.3	24.7	91.3	0.16	24.5	91.5
6.4	24.7	94.8	0.20	35.1	91.7
6.5	24.7	96.7	0.21	45.5	91.9

B. ROC curve of HbA1c in diagnosing diabetes (2hPG ≥ 200 mg/dL)



HbA1c, %	SEN, %	SPE, %	J Value	PPV, %	NPV, %
5.5	78.0	34.7	0.13	16.8	90.4
5.6	78.0	44.5	0.23	19.1	92.3
5.7	78.0	50.2	0.28	20.9	93.1
5.8	76.3	63.4	0.40	26.0	94.1
5.9	69.1	69.3	0.38	27.5	93.0
6.0	60.4	79.0	0.39	32.6	92.2
6.1	57.4	86.9	0.44	42.5	92.4
6.2	41.5	89.6	0.31	40.2	90.1
6.3	31.6	93.3	0.25	44.2	89.0
6.4	24.4	95.7	0.20	49.0	88.3
6.5	24.4	97.6	0.22	63.5	88.5

C. ROC curve of FPG in diagnosing diabetes (2hPG ≥ 200 mg/dL)



FPG, mg/dL	SEN, %	SPE, %	J Value	PPV, %	NPV, %
100	100.0	40.5	0.41	22.1	100.0
105	96.9	57.3	0.54	27.7	99.1
110	93.1	75.2	0.68	38.7	98.5
115	83.9	82.7	0.67	44.9	96.8
120	50.6	89.7	0.40	45.2	91.5
126	42.7	95.3	0.38	60.5	90.8

Figure 4.2. Receiver Operating Characteristic Curves of Hemoglobin A1c and Fasting Plasma Glucose for Diagnosis of Diabetes among Heart Failure Patients. Asterisks indicate that area under the receiver operating characteristic curves of fasting plasma glucose and hemoglobin A1c for diagnosis of diabetes defined by 2-hour plasma glucose (≥ 200 mg/dL) were significantly different. 2hPG = 2-hour plasma glucose; ACU; area under the curve; FPG; fasting plasma glucose; HbA1c = hemoglobin A1c; NPV = negative predictive value; PPV = positive predictive value; SEN = sensitivity; SPE = specificity.

CHAPTER 5

HIGH ADHERENCE TO THE DIETARY APPROACHES TO STOP HYPERTENSION DIET IS ASSOCIATED WITH LOW LEVELS OF INSULIN RESISTANCE AMONG COMMUNITY-DWELLING HEART FAILURE PATIENTS: A NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY ANALYSIS [4]

---

[4] Ishikawa Y, Laing EM, Anderson AK, Zhang D, Kindler JM, Trivedi-Kapoor R, Sattler ELP. Submitted to American Journal of Clinical Nutrition, 10/06/2021.

Abstract

Background

Heart failure (HF) patients are at risk of developing type 2 diabetes. Adherence to the Dietary Approaches to Stop Hypertension (DASH) diet has shown to improve insulin resistance in populations without HF. Given the complexity of HF pathophysiology and common drug-nutrient interactions, it is unknown whether positive effects of the DASH diet on insulin resistance persist among HF patients.

Objective

This study examined the association between adherence to the DASH diet and insulin resistance among U.S. adults with HF.

Methods

Using data from National Health and Nutrition Examination Survey 1999-2016 cycles, we included 348 individuals aged 20+ years with HF and no history of diabetes. Participants were classified by DASH diet adherence index quartiles: quartile 1 indicated the lowest and quartile 4 indicated the highest adherence. The highest level of insulin resistance was defined by the upper tertile of the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). Associations between level of insulin resistance and DASH diet adherence and its linear trends were examined using logistic regressions.

Results

Trend analyses showed that participants in upper DASH diet adherence index quartiles were more likely older, female, non-Hispanic white, of normal weight, and had lower levels of fasting insulin than those in lower quartiles. Median values of HOMA-IR from lowest to highest DASH diet adherence index quartiles were 3.1 (interquartile range, 1.8-5.5), 2.9 (1.7-5.6), 2.1 (1.1-3.7), and 2.1 (1.3-3.5). Multivariable logistic analyses indicated that participants with the highest compared to the lowest DASH adherence showed 77.1% lower odds of having the highest level of insulin resistance (0.229, 95% confidence interval: 0.073-0.716; p = 0.017 for linear trend).

Conclusions

High levels of adherence to the DASH diet were associated with lower insulin resistance among community-dwelling HF patients in the U.S. Heart healthy dietary patterns likely protect HF patients from developing type 2 diabetes.

Introduction

Heart failure (HF) is a complex clinical syndrome of neurohormonal abnormalities and metabolic alterations, and presents as one of the leading causes of hospital readmissions and mortality, affecting over 6.2 million Americans at an associated medical cost of $30.7 billion in 2012 (3). Heart failure patients are at risk of developing type 2 diabetes due to compensatory mechanisms of cardiac dysfunction which increases circulating levels of plasma free fatty acids, proinflammatory cytokines, and reactive oxygen species, leading to the development of insulin resistance (6, 13). Patients with coexisting HF and type 2 diabetes face increased clinical challenges related to morbidity and mortality in comparison to patients with HF alone (9), suggesting the need for cost-effective strategies to prevent or delay new-onset type 2 diabetes in HF patients.

Evidence-based guidance from the American Diabetes Association calls for adherence to healthy dietary patterns as a strategy to prevent the development of type 2 diabetes, including through consumption of the Dietary Approaches to Stop Hypertension (DASH) diet (269). The DASH dietary pattern, which encourages consumption of vegetables, fruits, whole grains, nuts, legumes, seafood, poultry, and low-fat dairy products while limiting red and processed meat, added sugars, and sodium (1,500–2,300 mg/day) (251), has shown to improve insulin resistance in clinical trials that included individuals without established HF (28-30). Compared to individuals without HF, HF patients are more vulnerable to insulin resistance due to HF pathophysiology and medication-induced nutrient imbalances which are known to impair insulin secretion and signaling regulation (13, 150, 310-312). Due to the complexity of HF pathophysiology, it is currently unclear whether adherence to the DASH diet shows similar effects on insulin resistance among HF patients as observed among non-HF patients. Previous studies have shown positive effects of DASH diet consumption on HF-related outcomes in populations with HF. Among female patients with HF in the Women's Health Initiative study, DASH diet consumption reduced the odds of mortality by 16% after a median follow-up of 4.6 years (257). In addition, small-scale randomized controlled DASH diet feeding trials have shown improvements in systolic and diastolic blood pressure, oxidative stress, cardiac energy metabolism, cardiac functional outcomes, and exercise tolerance (258-261). These trials further demonstrated trends towards improvements in patients' quality of life and a reduction in recurrent hospital admissions among individuals with HF after DASH diet consumption (262). Since there are no studies examining the effect of DASH diet consumption on insulin resistance among HF patients, epidemiological evidence on such associations is warranted to indicate the direction of future clinical trials regarding diabetes prevention and management in HF.

This secondary data analysis aimed to examine the relationship of adherence to the DASH diet with the level of insulin resistance among U.S. community-dwelling HF patients. We hypothesized that greater adherence to the DASH diet would be associated with lower levels of insulin resistance.

Methods

Study Design and Population

This cross-sectional study was a secondary analysis of National Health and Nutrition Examination Survey (NHANES) data between 1999 and 2016. The NHANES is an ongoing survey that uses a multistage, stratified sampling design to include a nationally representative sample of the civilian, non-institutionalized population in the U.S. The NHANES study protocols were approved by the research ethics boards of the National Center for Health Statistics (NCHS), and all participants provided written informed consent before the data collection. The survey design and sampling methods have been described in detail elsewhere (276).

The analytic sample included adults aged 20+ years with a self-reported physician diagnosis of HF. Participants were excluded from the analyses if they 1) did not attend the mobile examination center (MEC) morning session, 2) had incomplete data on fasting plasma glucose and insulin to calculate the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), 3) had a physician diagnosis of diabetes or used diabetes medications, 4) were pregnant, or 5) showed implausible energy intakes (gender-specific < 1st and > 99th percentiles of energy intake per day) (313). We only included participants who were randomly selected to attend the MEC morning session according to NHANES sampling procedures because of the availability of clinical parameters for fasting plasma glucose and insulin needed for the calculation of HOMA-IR. Any potential for selection bias was minimized by applying appropriate sample weights for those who attended the MEC morning session in our analysis in order to account for the complex, multistage, probability sampling design (283).

Assessment of Adherence to the DASH Diet

Daily total energy and nutrient intake from foods and beverages were estimated based on cycle-specific versions of the U.S. Department of Agriculture Food and Nutrition Database for Dietary Studies (FNDDS). Food group intakes were calculated using MyPyramid Equivalents and FNDDS databases. Usual dietary intake was estimated based on the National Cancer Institute (NCI) method to minimize measurement error (314), and estimations were adjusted for age, gender, race/ethnicity, body mass index (BMI), 24-hour dietary recalls (first recall administered during the MEC session or second recall administered by phone 3-10 days later), and the day-of-week of 24-hour recall (Monday-Thursday or Friday-Sunday). The DASH diet index scores were calculated using scoring criteria developed by Fung et al. (315), which scores eight food groups and nutrients to derive a total score ranging from 8-40, with higher values indicating better adherence to the DASH diet (Appendix C.1). Participants were classified by DASH diet index score quartiles according to a previous study (257): participants in quartile 1 indicated the lowest level and those in quartile 4 indicated the highest level of DASH diet adherence.

Assessments of Insulin Resistance

The following equation was used to calculate HOMA-IR: HOMA-IR = [fasting plasma glucose (nmol/L)*fasting insulin (μIU/mL)/22.5] (316). Participants were divided into tertiles of HOMA-IR (tertile 1: $\leq$ 1.71, tertile 2: 1.72-3.58; tertile 3: $\geq$ 3.59), with tertile 3 representing the highest level of insulin resistance. This approach is commonly practiced given the absence of an established cutoff point for HOMA-IR (317). Previous research has shown that the upper HOMA-IR tertile, compared to the lowest tertile, independently predicted incidence of type 2 diabetes (318).

Statistical Analysis

Survey analysis procedures with appropriate sample weights were used to account for the complex, multistage, probability sampling design and to produce nationally representative estimates of the U.S. civilian, non-institutionalized population (283). Participant characteristics were summarized using means and standard errors (SE) for continuous variables with a normal distribution, medians and interquartile ranges (IQR) for continuous variables with a non-normal distribution, and percentages for categorical variables. Trends of differences in participant characteristics across the DASH diet index quartiles were examined using general linear models for continuous variables with a normal distribution. For continuous variables with a non-normal distribution, a log transformation was applied before trend analyses to achieve an approximately normal distribution. For categorical variables, differences and trends in proportions of participant characteristics across the DASH diet index quartiles were examined using the Rao-Scott F adjusted chi-square tests and logistic regression models, respectively. Associations of adherence to the DASH diet to the level of insulin resistance and its linear trends were examined using logistic regression models. Model 1 was not adjusted. Model 2 was adjusted for age, gender, and race/ethnicity. Model 3 was further adjusted for BMI, dietary energy, waist circumference, smoking, triglyceride levels, high-density lipoprotein (HDL)-cholesterol levels, history of liver disease, and history of stroke. While dietary energy was intentionally selected into the model because of a potentially confounding effect (319), the other variables were selected because of significant associations with insulin resistance in the unadjusted models (Appendix C.2). Variance inflation factors (VIF) < 2.5 in multivariable logistic regression models were considered to confirm the absence of multicollinearity (320). All statistical tests were 2-sided, and P values < 0.05 were considered statistically significant. No imputation was needed according to the NHANES analytic guideline since no variables had ≥ 11% of missing data (283). No correction for multiple statistical tests was applied because this study aimed to test preplanned hypotheses. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary NC) and R statistical software version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Analytic Sample

The analytic sample selection is shown in Appendix C.3. Among 92,062 participants, 1,705 participants were aged 20+ years and had a history of HF. After excluding participants who did not attend the MEC morning session (n = 919), who had incomplete measurements of HOMA-IR (n = 78), who had a history of diabetes or diabetes medication use (n = 288), were pregnant (n = 2), or showed implausible dietary data (n = 70), a total of n = 348 HF patients were included in the analyses. The prevalence of HF among included participants was 2.4% (95% confidence interval [CI], 2.2-2.7%) which is comparable to previous prevalence estimates of HF in the U.S. population (3). Compared to excluded participants, included participants were significantly more likely male (57.2% vs. 48.6%; $p = 0.024$) and non-Hispanic white (80.6% vs. 69.4%; $p = 0.001$), and they were less likely to report hypertension (66.1% vs. 76.6%; $p = 0.005$) (Appendix C.4).

Sociodemographic and medical characteristics of study participants across quartiles of the DASH diet adherence index are shown in Table 5.1. The DASH diet index scores ranged from 11-37 points among all participants (11-20 points in quartile 1; 21-24 points in quartile 2; 25-27 points in quartile 3; 28-37 points in quartile 4). Linear trend analyses showed that there were increasing linear trends across DASH diet adherence index quartiles in age (mean age ± SE: 55.7 ± 1.9 years in quartile 1, 62.1 ± 1.6 years in quartile 2, 69.9 ± 0.8 years in quartile 3, 72.4 ± 1.7 years in quartile 4; $p < 0.001$ for trend), proportion of female participants (33.1%, 39.1%, 45.6%, and 58.7%, respectively; $p < 0.001$), proportion of non-Hispanic whites (59.7%, 78.8%, 80.5%, and 91.8%, respectively; $p < 0.001$), proportion of participants with normal weight (22.6%, 13.5%, 42.5%, and 36.6%, respectively; $p < 0.001$), systolic blood pressure (mean systolic blood pressure ± SE: 122.4 ± 3.1 mm Hg, 127.2 ± 1.8 mm Hg, 127.4 ± 2.7 mm Hg, and 132.3 ± 2.8 mm Hg, respectively; $p = 0.041$), and proportion of participants with a history of angina (13.9 %, 22.4%, 44.0%, and 29.9%, respectively; $p = 0.007$). In addition, there were decreasing linear trends across DASH diet adherence index quartiles in diastolic blood pressure (mean diastolic blood pressure ± SE: 70.9 ± 2.2 mm Hg, 69.3 ± 0.8 mm Hg, 67.2 ± 1.7 mm Hg, and 62.6 ± 1.9 mm Hg, respectively; $p = 0.008$), fasting insulin levels (median fasting insulin levels [IQR]: 11.8 [7.1-21.3] uU/mL, 11.7 [7.3-19.6] uU/mL, 8.3 [4.5-14.0] uU/mL, and 8.2 [5.7-11.4] uU/mL, respectively; $p = 0.021$), and smoking rates (51.3%, 26.1%, 21.4%, and 4.3%, respectively; $p < 0.001$). No linear trend across DASH diet adherence index quartiles was observed for fasting plasma glucose (median fasting plasma glucose [IQR]: 101.8 [95.2-108.1] mg/dL, 105.0 [96.3-116.5] mg/dL, 103.2 [93.7-112.1] mg/dL, and 106.0 [95.8-116.4] mg/dL, respectively; $p = 0.559$).

Intake of Nutrient and Food Groups across DASH Diet Adherence Index Quartiles

The intake of nutrients and food groups across quartiles of the DASH diet adherence index is described in Appendix C.5. Participants with high levels of DASH diet adherence showed higher intakes of dietary fiber, vitamin E, vitamin A, vitamin B6, folate, vitamin C, calcium, magnesium, and potassium, while they showed lower intakes of total energy, protein, total fat, saturated, monounsaturated, and polyunsaturated fatty acids, cholesterol, and carbohydrates, in comparison to participants with low levels of DASH diet adherence. Participants with high levels of DASH diet adherence showed higher protein-energy and carbohydrate-energy ratios but a lower total fat-energy ratio, in comparison to participants with low levels of adherence to the DASH diet. As expected, participants with high levels of DASH diet adherence showed comparably higher intakes of fruits, vegetables, nuts, and legumes, whole grains and lower intakes of red and processed meats, discretionary oil and solid fat, and sweetened beverages.

Associations between HOMA-IR Levels and DASH Diet Adherence

Results of the logistic regression analyses to examine associations between HOMA-IR levels and DASH diet adherence index quartiles are presented in Figure 5.1. Median values of HOMA-IR were 3.1 (IQR, 1.8-5.5) in quartile 1, 2.9 (1.7-5.6) in quartile 2, 2.1 (1.1-3.7) in quartile 3, and 2.1 (1.3-3.5) in quartile 4. Frequencies of the highest level of insulin resistance in DASH diet adherence index quartiles were 45.9% in quartile 1, 40.7% in quartile 2, 25.6% in quartile 3, and 21.6% in quartile 4. In the unadjusted Model 1, participants with the highest level of DASH diet adherence showed the lowest odds of having the highest level of insulin resistance, compared to those with the lowest level of DASH diet adherence (odds ratio [OR] 0.324, 95% CI 0.129-0.818). Linear trends for improved insulin resistance were observed with increasing levels of DASH diet adherence (p = 0.005). Similar findings were observed after adjusting for demographic characteristics (Model 2), where participants with the highest level of DASH diet adherence had the lowest odds of having the highest level of insulin resistance in comparison to those with the lowest level of DASH diet adherence (adjusted OR 0.323, 95% CI 0.106-0.986). In model 2, linear trends for improved insulin resistance were observed with increasing levels of DASH diet adherence (p = 0.017). After further adjusting for BMI, waist circumference, smoking status, dietary energy levels, triglyceride levels, HDL-cholesterol levels, and history of stroke, similar findings were observed (Model 3; adjusted OR 0.229, 95% CI 0.073-0.716, p for linear trend = 0.017). Obese participants showed increased odds of the highest level of insulin resistance compared to those with normal BMI, and participants with dyslipidemia showed increased odds of the highest level of insulin resistance in comparison to those with normal lipid levels (Table 5.2). In contrast, participants who were currently smoking had decreased odds of the highest level of insulin resistance in comparison to their counterparts. No multicollinearity (Model 2: VIF = 1.1; Model 3: VIF = 1.4) and interaction were detected.

Discussion

In this sample of community-dwelling HF patients in the U.S., good adherence to the DASH diet was independently associated with low levels of insulin resistance. To our knowledge, this is the first study reporting an association of DASH diet adherence with insulin resistance in HF patients.

Our finding of the inverse association between adherence to the DASH diet and insulin resistance in HF patients is consistent with previously published observational studies in individuals without established HF (321-323). Cross-sectional studies have shown that adherence to the DASH diet was inversely correlated with HOMA-IR among patients without diabetes (321, 322). In a cohort study with 3-year follow-up, individuals with the highest levels of DASH diet adherence had 51% lower odds of developing insulin resistance in comparison to those with the lowest levels of DASH diet adherence. These findings were independent of demographic characteristics, anthropometric data, physical activity levels, and smoking status (323).

In contrast to observational studies, randomized controlled trials (RCTs) provided inconclusive results regarding the effects of DASH diet-based nutritional counseling on insulin resistance in populations without established HF (28-30, 102). A meta-analysis of 4 RCTs including 869 individuals without established HF demonstrated no effect of DASH diet-based nutritional counseling on HOMA-IR (102). However, more recently published RCTs showed that DASH diet-based nutritional counseling significantly reduced HOMA-IR values in overweight and obese individuals with primary arterial hypertension (28), polycystic ovary syndrome (29), and nonalcoholic fatty liver disease (30). These observed differences may be attributed to the fact that the meta-analysis was published in 2013 and the results of more recently published RCTs were not included. In addition, given that the meta-analysis included healthy individuals and individuals with pre-existing conditions, the results of the meta-analysis are unlikely to be representative of any effects observed among typically multimorbid HF patients.

The mechanisms underlying the effects of DASH diet consumption on insulin resistance may be explained by previous literature that suggests consumption of key food groups and nutrients emphasized by the DASH diet to have positive effects on the insulin-dependent glucose transportation translocation process. First, whole-grains, nuts, and legumes are well-known sources of digestion-resistant starch, a type of carbohydrate that cannot be digested and absorbed in the small intestine but is fermented by microbiota in the colon (324). Digestion-resistant starch consumption has shown to increase the glucose-dependent insulinotropic polypeptide (325), which in turn promotes insulin-dependent glucose transporter translocation in skeletal muscle (326). Second, high red meat consumption, which the DASH diet limits, may independently exacerbate insulin resistance since excess intake of arginine and alanine from red meat accelerates glucagon secretion, which impedes insulin action and consequently causes hyperinsulinemia (327). In addition, the DASH diet may positively influence HF pathophysiology associated with the development of insulin resistance. Deficiencies in essential macrominerals, including calcium, potassium, and magnesium, are often observed among HF patients due to HF pathophysiology and medication-induced micronutrient imbalances (150), and a lack of these macrominerals leads to impairments of insulin secretion and signaling regulation (310-312). Adherence to the DASH diet likely helps ensure adequate intake of these micronutrients and consequently to maintain the regulation of the insulin-dependent glucose transportation translocation (328-330). Furthermore, adherence to the DASH diet may delay or prevent insulin resistance through attenuation of the activated sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) (331) among HF patients who have activated SNS and increased RAAS activity to compensate for reduced cardiac output (40). Activation of these neurohormonal pathways may cause elevation of plasma free fatty acid levels and imbalance of reactive oxidative species production, resulting in impaired insulin-dependent glucose transporter translocation (13, 332). Although effects of the DASH diet on neurohormonal activities remain unknown among HF patients, a clinical trial among overweight and obese patients without HF demonstrated that a DASH diet-based nutritional education intervention reduced arterial norepinephrine concentration and microneurographic nerve recordings of muscle sympathetic nerve activity, an indicator of the SNS activity (333). A potential mechanism for positive effects of the DASH diet on neurohormonal pathways may involve reduced dietary sodium intake, which protects sympathetic-regulatory function against factors associated with increased SNS activities, including aldosterone or angiotensin II (334). A dietary strategy with sole emphasis on aggressive reduction of dietary sodium intake, however, is controversial in HF management. Randomized controlled trials did not support beneficial effects of aggressive sodium reduction on HF outcomes, including congestion symptoms, New York Heart Association functional class, hospital (re)admissions, health-related quality of life, and mortality (230-232). These findings highlight the limitation of a single nutrient strategy and underscore the importance of generating evidence that examines effects of heart-healthy dietary pattern consumption on HF prognosis.

The results of our study should be considered with several limitations. Over 1,300 participants with HF were excluded from our analyses, which may create the impression of selection bias. However, approximately 70% of participants were excluded due to NHANES sampling procedures which randomly select a subsample to be included in the MEC morning session to obtain the clinical parameters essential to our analyses. This subsample is representative of the general U.S. population. We estimated HF prevalence among the MEC morning session subsample at 2.4% which was comparable to prevalence estimates of HF among U.S. adults (2.2%) (3). Although we observed differences in characteristics between included and excluded participants with HF, none of these characteristics were associated with insulin resistance, and therefore, any potential selection bias effect should be considered minimal. Missing values for covariates in the multivariate logistic regression models may have affected the statistical inference of our results; nevertheless, no covariate in the models had 10% or more missing data (Appendix C.6), and therefore, no imputation of missing values was needed, as recommended by NCHS (283). Despite these limitations, our study used a nationally representative sample with standardized data collection methods, which produced highly generalizable results for community-dwelling HF patients in the U.S.

In conclusion, in a sample of community-dwelling HF patients in the U.S., higher levels of adherence to a DASH diet were associated with lower insulin resistance. Clinical DASH feeding trials are needed to examine causal effects of adherence to the DASH diet on the prevention of insulin resistance and the development of type 2 diabetes among patients with HF.

Table 5.1. Sociodemographic and Medical Characteristics of U.S. Adults with Heart Failure

		DASH Diet Adherence Index				
Characteristics	**ALL**	**Quartile 1**	**Quartile 2**	**Quartile 3**	**Quartile 4**	**P Value[1]**
DASH Diet Score Range	11 - 37	11 - 20	21 - 24	25 - 27	28 - 37	
Participants, No.	348	76	109	82	81	
Sociodemographic Characteristics						
Age, Mean (SE), Years	65.3 (0.9)	55.7 (1.9)	62.1 (1.6)	69.9 (0.8)	72.4 (1.7)	< 0.001
Female, %	44.2	33.1	39.1	45.6	58.7	< 0.001
Race/Ethnicity, %						
Non-Hispanic White	78.6	59.7	78.8	80.5	91.8	< 0.001
Non-Hispanic Black	10.5	35.7	5.2	6.0	1.5	
All Hispanic	6.6	0.9	11.6	7.0	4.0	
Other	4.3	3.7	4.3	6.5	2.7	
Physical Examination, Laboratory Values, and Behavioral Factors						
BMI Categories, %						
Normal Weight	27.8	22.6	13.5	42.5	36.6	< 0.001
Overweight	36.1	27.0	47.4	30.7	34.1	
Obese	36.0	50.4	39.1	26.8	29.2	
Abnormal Abdominal Fat, %[2]	65.9	67.3	74.8	55.7	62.5	0.180
SBP, Mean (SE), mm Hg	127.6 (1.6)	122.4 (3.1)	127.2 (1.8)	127.4 (2.7)	132.3 (2.8)	0.041
DBP, Mean (SE), mm Hg	67.4 (0.9)	70.9 (2.2)	69.3 (0.8)	67.2 (1.7)	62.6 (1.9)	0.008
Fasting Insulin, Median (IQR), uU/mL[3]	9.5 (5.9-15.9)	11.8 (7.1-21.3)	11.7 (7.3-19.6)	8.3 (4.5-14.0)	8.2 (5.7-11.4)	0.021
Fasting Plasma Glucose, Median (IQR), mg/dL[3]	104.0 (95.9-115.1)	101.8 (95.2-108.1)	105.0 (96.3-116.5)	103.2 (93.7-112.1)	106.0 (95.8-116.4)	0.559
Serum Triglyceride, Median (IQR), mg/dL[3]	128.0 (88.7-169.5)	127.7 (77.2-168.4)	133.9 (97.0-196.0)	116.8 (81.9-170.3)	127 (83.4-149.8)	0.266
High Serum Triglycerides Levels, %[2]	34.7	35.1	44.0	30.8	25.8	0.124
HDL-Cholesterol, Median (IQR), mg/dL[3]	46.9 (39.4-58.5)	44.4 (35.8-55.1)	45.7 (39.7-59.0)	47.4 (40.1-58.3)	49.6 (40.4-70.2)	0.018
Low HDL-Cholesterol Levels, %[2]	35.1	42.5	35.5	30.1	33.5	0.326
LDL-Cholesterol, Mean (SE), mg/dL	106.5 (2.2)	99.6 (4.6)	109.6 (2.5)	108.0 (3.5)	106.4 (4.2)	0.528
High LDL-Cholesterol Levels, %[2]	53.1	50.3	53.6	55.8	51.9	0.878
Smoking, %	24.6	51.3	26.1	21.4	4.3	< 0.001
Medical History, %						
Angina	27.8	13.9	22.4	44.0	29.9	0.007
Coronary Heart Disease	38.4	39.2	30.9	46.3	39.7	0.439
Myocardial Infarction	44.5	41.2	52.9	46.3	34.1	0.283
Hypertension	67.7	63.2	61.1	80.4	67.2	0.272

Stroke	21.3	18.7	17.5	31.2	18.5	0.614
Medication Use, %						
Angiotensin Converting Enzyme Inhibitors	31.6	36.1	37.5	23.7	28.0	0.142
Angiotensin II Receptor Blockers	8.7	8.6	9.2	7.8	9.2	1.000
β-blockers	47.6	47.2	38.8	52.6	54.8	0.213
Loop Diuretics	35.8	30.6	44.6	28.3	35.8	0.810

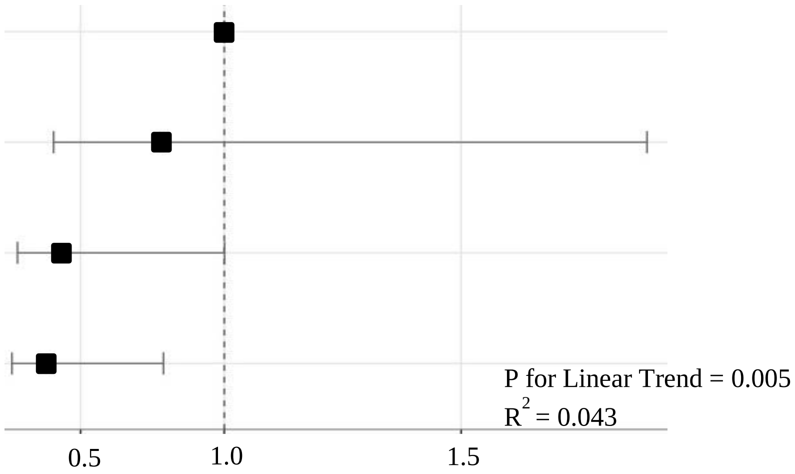
[1] For continuous variables p-values indicate significance of linear trend over the DASH diet index quartiles groups using survey-weighted general linear models. For categorical variables p-values indicate significance of linear trend over the DASH diet index quartiles groups using survey-weighted logistic regressions.; [2]Abnormal abdominal fat was defined as waist circumference ≥ 102 cm for male or ≥ 88 cm for female. High serum triglyceride levels were defined as serum triglyceride levels ≥ 150 mg/dL. Low HDL-cholesterol levels were defined as HDL-cholesterol levels < 40 mg/dL for male or < 50 mg/dL for female. High LDL-cholesterol levels were defined as LDL-cholesterol levels ≥100 mg/dL.; [3]P-values were assessed after log-transformations.; Abbreviations: BMI, body mass index; CKD, chronic kidney disease; DASH, dietary approaches to stop hypertension; DBP, diastolic blood pressure; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; No, number; SDP, systolic blood pressure; SE, standard error.

Table 5.2. Associations of Selected Characteristics with the Highest Level of Insulin Resistance among Heart Failure Patients in the Multivariable Logistic Regression Model

	AOR (95% CI)	**P-Value**	**P for Interaction**
DASH Diet Adherence Index (Ref. Quartile 1)			
Quartile 2	0.512 (0.200-1.310)	0.161	
Quartile 3	0.453 (0.151-1.360)	0.157	
Quartile 4	0.229 (0.073-0.716)	0.012	
Age ≥ 65 Years (Ref. < 65 Years)	1.034 (0.490-2.182)	0.930	0.170
Male (Ref. Female)	0.540 (0.196-1.490)	0.232	0.429
Racial/Ethnic Minorities (Ref. Non-Hispanic White)	1.383 (0.597-3.208)	0.447	0.958
Dietary Energy (Ref. Tertile 1; < 1560 kcal)			0.636
Tertile 2 (1560-1949 kcal)	0.889 (0.343-2.300)	0.807	
Tertile 3 (≥ 1950 kcal)	1.811 (0.572-5.739)	0.310	
Current Smoker (Ref. Not Smoking)	0.202 (0.073-0.560)	0.002	0.543
BMI Categories (Ref. Normal Weight, < 25 kg/m^2)			0.925
Overweight (25-29 kg/m^2)	2.976 (0.615-14.407)	0.174	
Obese (≥ 30 kg/m^2)	7.724 (1.227-48.606)	0.030	
Abnormal Abdominal Fat (Ref. Normal Abdominal Fat)	1.798 (0.544-5.945)	0.333	0.768
High Serum Triglyceride Levels (Ref. Normal Level)	2.273 (1.016-5.087)	0.046	0.436
Low HDL-Cholesterol Levels (Ref. Normal Level)	2.504 (1.166-5.378)	0.019	0.353
History of Stroke (Ref. No History)	0.693 (0.277-1.732)	0.430	0.588

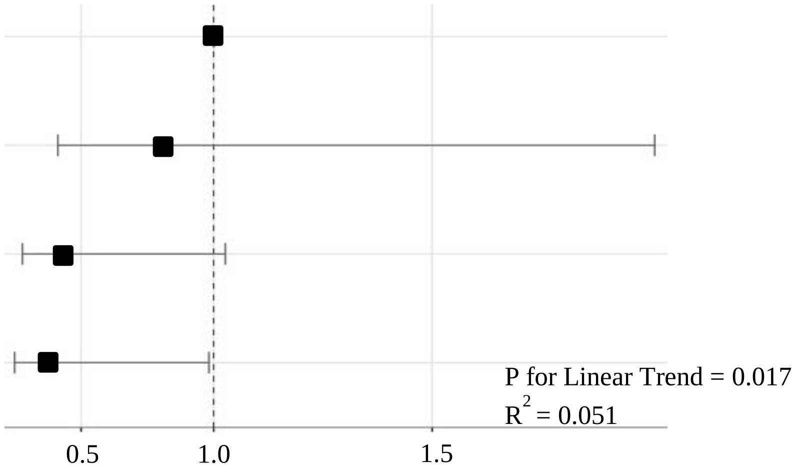
R-square was 0.306.; DASH diet adherence index Quartile 1 indicates the lowest level and quartile 4 indicates the highest level of adherence. Abnormal abdominal fat was defined as waist circumference ≥ 102 cm for male or ≥ 88 cm for female. High serum triglyceride levels were defined as serum triglyceride levels ≥ 150 mg/dL. Low HDL-cholesterol levels were defined as HDL-cholesterol levels < 40 mg/dL for male or < 50 mg/dL for female. Abbreviations: AOR, adjusted odds ratio; BMI, body mass index; Ref. reference group.

Model 1	**OR (95% CI)**
Quartile 1	Reference
Quartile 2	0.809 (0.370-1.769)
Quartile 3	0.406 (0.165-1.001)
Quartile 4	0.324 (0.129-0.818)



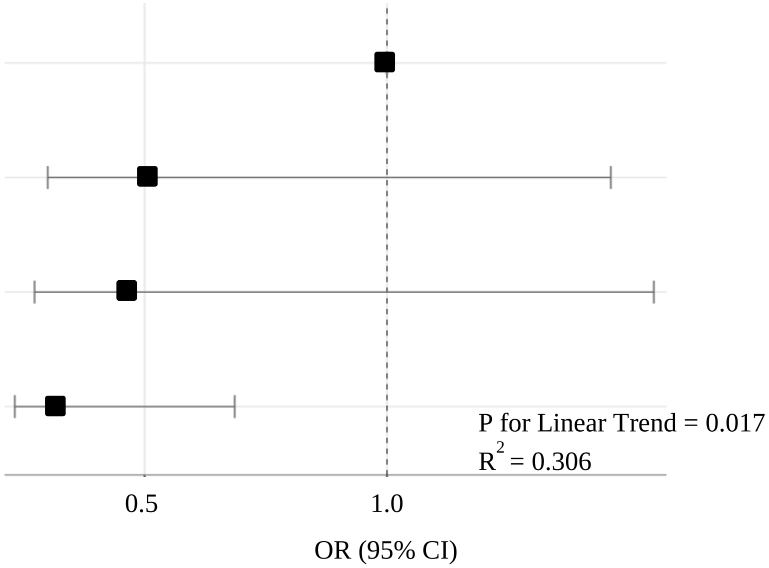
P for Linear Trend = 0.005
$R^2 = 0.043$

Model 2	**AOR (95% CI)**
Quartile 1	Reference
Quartile 2	0.834 (0.379-1.837)
Quartile 3	0.408 (0.161-1.034)
Quartile 4	0.323 (0.106-0.986)



P for Linear Trend = 0.017
$R^2 = 0.051$

Model 3	**AOR (95% CI)**
Quartile 1	Reference
Quartile 2	0.512 (0.200-1.310)
Quartile 3	0.453 (0.151-1.360)
Quartile 4	0.229 (0.073-0.716)



	DASH Diet Adherence Index			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Participants, No	76	109	82	81
HOMA-IR, median (IQR)	3.1 (1.8-5.5)	2.9 (1.7-5.6)	2.1 (1.1-3.7)	2.1 (1.3-3.5)
Participants with the Highest Level of IR, No. (%)	32 (45.9)	42 (40.7)	24 (25.6)	17 (21.6)

Figure 5.1. Odds Ratios of the Level of Insulin Resistance across the Dietary Approaches to Stop Hypertension Diet Adherence Index Quartiles among Heart Failure Patients - Quartile 1 indicates the lowest level and quartile 4 indicates the highest level of adherence. Odds ratio and p value for linear trends were examined by logistic regressions with survey analysis procedures. Model 1 was the unadjusted model. Model 2 was adjusted for age (< 65 years or ≥ 65 years), gender (female or male), and race/ethnicity (non-Hispanic white or other racial minorities). Model 3 was further adjusted for body mass index (< 25 kg/m^2, 25-29 kg/m^2, or ≥ 30 kg/m^2), waist circumference (normal [< 102 cm for male; < 88 cm for female] or abnormal abdominal fat [≥ 102 cm for male; ≥ 88 cm for female]), current smoker (yes or no), dietary energy (< 1560 kcal, 1560-1949 kcal, or ≥ 1950 kcal), triglyceride levels (normal [< 150 mg/dL] or high levels [≥ 150 mg/dL]), high-density lipoprotein-cholesterol levels (normal [≥ 40 mg/dL for male; ≥ 50 mg/dL for female] or low levels [< 40 mg/dL for male; < 50 mg/dL for female]), and history of stroke (yes or no). Abbreviations: AOR, adjusted odds ratio; CI,

confidence interval; DASH, Dietary Approaches to Stop Hypertension; HOMA-IR, homeostatic model assessment-insulin resistance; IQR, interquartile range; IR, insulin resistance; No, number; OR, odds ratio.

CHAPTER 6

SUMMARY AND CONCLUSIONS

Summary of Findings

The objective of this dissertation was to assess the burden of type 2 diabetes and provide evidence on improved ways to prevent type 2 diabetes in heart failure (HF) patients. The first dissertation study, presented in Chapter 3, assessed prevalence and trends of diagnosed and undiagnosed type 2 diabetes and prediabetes among U.S. community-dwelling adults with HF. We used a nationally representative sample of the U.S. civilian, non-institutionalized HF patients, and found more than 85% of participants to show signs of hyperglycemia. Prevalence estimates of diagnosed and undiagnosed type 2 diabetes among HF patients were 34.7% and 12.8%, respectively, which are 4- and 2-hold higher in comparison to the general U.S. population (280). Prediabetes affected 39.1% of HF patients. Prevalence estimates of type 2 diabetes were different across sociodemographic and health characteristics. Hispanics showed significantly higher prevalence estimates of diagnosed type 2 diabetes than non-Hispanic whites (52.1% vs. 20.1%, respectively; $P < 0.001$). In addition, prevalence estimates of diagnosed type 2 diabetes among HF patients with a history of stroke were significantly higher compared to prevalence estimates in their counterparts (69.4% vs. 24.4%, respectively; $P < 0.001$). Furthermore, we found that prevalence estimates of type 2 diabetes and prediabetes among U.S. community-dwelling HF patients did not change but remained at a high level between 2005 and 2016.

The second dissertation study, presented in Chapter 4, was conducted to compare diagnostic methods for diabetes among U.S. community-dwelling adults with HF and without a history of diabetes. In this study, 50 participants met at least 1 of 3 clinical criteria for diabetes, but the overlap in diabetes case detection among the criteria was very small: 2-hour plasma glucose (2hPG) after oral glucose tolerance test (OGTT) alone identified 70.5% of patients, while hemoglobin A1c (HbA1c) alone identified only 27.0% of patients. The proportion of individuals being diagnosed with diabetes by all 3 methods was 12.3%. Our study findings were consistent with previous studies among patients with coronary artery disease (24) and HF (305). In addition, the performance of HbA1c in identifying diabetes was suboptimal and significantly lower than the performance of fasting plasma glucose, resulting in 76% of patients to remain undiagnosed if the currently recommended HbA1c cutoff point of 6.5% was used to screen for diabetes. The sensitivity and specificity of HbA1c was maximized at 6.1%. Our study provided new evidence on the differential performance of HbA1c, FPG, and 2hPG for diagnostic screening in HF patients, and findings suggest blood glucose criteria may be preferred over HbA1c to screen for diabetes among HF patients without a history of diabetes. In addition, a HbA1c cutoff point at 6.1% as criterion for diabetes diagnosis should be considered for HF patients if FPG and 2hPG are impractical in the target population.

The third dissertation study, presented in Chapter 5, was conducted to examine the association between adherence to the Dietary Approaches to Stop Hypertension (DASH) diet and the severity of insulin resistance among U.S. community-dwelling HF patients without a history of diabetes, and found that greater adherence to the DASH diet was associated with lower levels of insulin resistance. Participants with the highest DASH adherence, compared to those with the lowest level of adherence, had higher intakes of essential nutrients, including macrominerals which are frequently deficient among HF patients due to HF pathophysiology and medication-induced mineral imbalances, but are important to regulate insulin-dependent glucose transportation translocation processes and may therefore play a significant role in the prevention of diabetes in this population. In addition, in comparison to participants with the lowest DASH adherence, participants with the highest DASH adherence had lower intakes of red and processed meat, which are known to accelerate the development of insulin resistance (327), suggesting that eating less red and processed meat may prevent or delay new-onset diabetes in this population. We found that median values of HOMA-IR from the lowest to highest DASH adherence groups were 3.1 (Interquartile range, 1.8-5.5), 2.9 (1.7-5.6), 2.1 (1.1-3.7), and 2.1 (1.3-3.5), respectively. Frequencies of high insulin resistance from the lowest to highest DASH adherence groups were 45.9%, 40.7%, 25.6%, and 21.6%, respectively. In addition, HF participants with the highest compared to the lowest DASH adherence had 77.1% lower odds of having the high levels of insulin resistance.

Strengths and Limitations

There are several limitations to the research presented. The cross-sectional study design using National Health and Nutrition Examination Survey (NHANES) data precludes drawing temporal and causal relationships in our findings. In the first dissertation study, presented in Chapter 3, causality between prevalence estimates of type 2 diabetes and prediabetes and sociodemographic and health characteristics cannot be determined. In the second dissertation study, presented in Chapter 4, assumptions about the effects of low diagnostic performance of HbA1c in identifying diabetes on clinical HF outcomes cannot be made. In the third dissertation study, presented in Chapter 5, causal inferences between adherence to the DASH diet and the severity of insulin resistance cannot be drawn. Therefore, it is not possible to determine whether DASH diet consumption improves insulin resistance among HF patients based on a cross-sectional study. In addition, all self-reported information collected in the NHANES, including reported physician diagnoses of HF and diabetes, are subjected to recall bias. The NHANES datasets are limited in HF-related information, because these datasets were not intentionally designed to examine the HF population. A lack of HF-related information may limit our understanding of analytic sample characteristics in relation to HF characteristics, comparability to other HF studies, and magnitude of our findings, particularly with regard to HF subtypes and severity of symptoms. For example, patients with coexisting diabetes and preserved ejection fraction (left ventricular ejection fraction > 40%) have higher mortality rates in comparison to patients with coexisting diabetes and reduced ejection fraction (left ventricular ejection fraction ≤ 40%) (81). Furthermore, HF patients with more severe symptomatic status, defined as New York Heart Association (NYHA) Class III, have a higher risk of developing new-onset diabetes, in comparison to HF patients with mild symptomatic status, defined as NYHA Class I (16), and these differences may have influenced our study results. Given that adverse clinical outcomes may be dependent on HF ejection fraction phenotype and severity of symptoms, subgrouping HF patients based on the HF characteristics would provide a better interpretation of study findings for clinical sub-populations.

Despite these limitations, using the NHANES data allowed for high generalizability to community-dwelling HF patients in the U.S. civilian, non-institutionalized population. Standardized interview, anthropometry, and laboratory data collection methods minimizes the random error associated with measurements, which increase validity of our findings. The findings of this dissertation add valuable epidemiological evidence on developing clinical preventive strategies to improve HF prognosis.

Clinical Implications and Recommendations for Future Research

The findings of this dissertation provide important clinical implications. The findings presented in Chapter 3 signify the extent of undiagnosed diabetes and prediabetes in the U.S. adult population and emphasize the need to improve diabetes screening efforts in at-risk HF patients. We found HF patients of Hispanic origin to be a particularly important target for these efforts. In comparison to non-Hispanic whites, racial minorities experience greater barriers to diabetes self-management and higher risks of diabetes complications due to inferior quality of diabetes care, including less frequent examinations of glycemia, blood pressure, and microvascular functions, caused by lower socioeconomic status and reduced access to care (288, 289). Future research in this area is needed to better understand details regarding characteristics associated with HF patients at risk for undiagnosed diabetes and prediabetes beyond our study findings. For example, it may be important to examine pathophysiological risk profiles associated with diabetes and prediabetes among HF patients, such as left ventricular ejection fraction and HF severity staging. Prospective cohort study data designed with the goal of improving HF care, such as the global congestive heart failure (G-CHF) registry (335), Change the Management of Patients with Heart Failure (CHAMP-HF) registry (336), European Society of Cardiology Heart Failure Long-Term (ESC-HF-LT) registry (337), Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) prospective observational study (338), would be best suited to close this knowledge gap.

The findings presented in Chapter 4 outlined limitations of using HbA1c as diagnostic criterion among U.S. HF patients without a history of diabetes and suggest use of blood glucose criteria, including FPG and 2hPG, in order to accurately determine a diagnosis of diabetes. The study also highlighted improved performance of HbA1c in diagnosing diabetes in HF patients if the cutoff point is lowered to 6.1%. Future research is needed to examine the performance of HbA1c, FPG, and 2hPG in diagnosing diabetes stratified by demographic and clinical sub-populations for a better understanding of the appropriateness of diagnostic measures in important subpopulations. For instance, it may be important to examine the receiver operating characteristic curve of HbA1c in diagnosing diabetes based on the status and severity of anemia among HF patients, because anemia, a highly prevalent comorbidity among HF patients (293), is known to systematically change HbA1c values irrespective of blood glucose levels (294-298). In addition, future research should examine the cost-effectiveness of lowered HbA1c cutoff points for a diagnosis of diabetes among HF patients, because lowering the HbA1c cutoff point may increase a chance of false positives and may therefore potentially lead to unnecessary preventive interventions when the actual risk of diabetes-related morbidity and mortality may be low. A cost-effectiveness simulation study, using the Markov simulation model developed by the Centers for Disease Control and Prevention and Research Triangle Institute International (339), should be conducted to examine the individual and societal health benefit of lowering HbA1c cutoff point among HF patients.

Lastly, the findings presented in Chapter 5 indicated greater adherence to the DASH diet to be independently associated with lower levels of insulin resistance and suggest the importance of following heart-healthy dietary patterns to prevent or delay new-onset type 2 diabetes among HF patients. In this study, higher intake of key macrominerals as a result of closer adherence to the DASH diet pattern among HF patients may compensate for HF pathophysiology and medication-induced deficiency of the macrominerals and therefore prevent diabetes development by improving insulin-dependent glucose uptake in target tissues. Future studies should implement randomized controlled DASH diet feeding trials to examine causal relationships between DASH diet consumption and improved insulin resistance among HF patients without history of diabetes. Adjusting for key confounding factors, including left ventricular ejection fraction and HF severity, is important since these factors likely affect the direction and magnitude of the causal relationships between DASH diet consumption and insulin resistance (98). Clinical and Translational Science Alliances may provide the essential infrastructure and facilitate the recruitment and enrollment of HF patients to conduct such a study (268).

REFERENCES

1. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, et al. 2017 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 Am Coll Cardiol 2017;70(6):776-803.
2. Kannel WB. Incidence and epidemiology of heart failure. Heart Fail Rev 2000;5(2):167-73.
3. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, et al. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. Circulation 2020:141(9):e139-596.
4. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail 2013;6(3):606-19.
5. Joffe SW, Webster K, McManus DD, Kiernan MS, Lessard D, Yarzebski J, Darling C, Gore JM, Goldberg RJ. Improved survival after heart failure: a community-based perspective. J Am Heart Assoc 2013;2(3):e000053.

6. Dunlay SM, Givertz MM, Aguilar D, Allen LA, Chan M, Desai AS, Deswal A, Dickson VV, Kosiborod MN, Lekavich CL, et al. Type 2 diabetes mellitus and heart failure, a scientific statement from the American Heart Association and Heart Failure Society of America. J Card Fail 2019;25(8):584-619.
7. Seferovic PM, Petrie MC, Filippatos GS, Anker SD, Rosano G, Bauersachs J, Paulus WJ, Komajda M, Cosentino F, de Boer RA, et al. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2018;20(5):853-72.
8. Dauriz M, Mantovani A, Bonapace S, Verlato G, Zoppini G, Bonora E, Targher G. Prognostic impact of diabetes on long-term survival outcomes in patients with heart failure: a meta-analysis. Diabetes Care 2017;40(11):1597-605.
9. Dauriz M, Targher G, Temporelli PL, Lucci D, Gonzini L, Nicolosi GL, Marchioli R, Tognoni G, Latini R, Cosmi F, et al. Prognostic impact of diabetes and prediabetes on survival outcomes in patients with chronic heart failure: a post-hoc analysis of the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca-Heart Failure) Trial. J Am Heart Assoc 2017;6(7):e005156.
10. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. Am J Cardiol 1972;30(6):595-602.
11. Greene SJ, Butler J. Primary prevention of heart failure in patients with type 2 diabetes mellitus. Circulation 2019;139(2):152-4.
12. Unnikrishnan R, Pradeepa R, Joshi SR, Mohan V. Type 2 diabetes: demystifying the global epidemic. Diabetes 2017;66(6):1432-42.

13. Ashrafian H, Frenneaux MP, Opie LH. Metabolic mechanisms in heart failure. Circulation 2007;116(4):434-48.

14. Rosano GM, Vitale C, Seferovic P. Heart failure in patients with diabetes mellitus. Card Fail Rev 2017;3(1):52-5.

15. Riehle C, Abel ED. Insulin signaling and heart failure. Circ Res 2016;118(7):1151-69.

16. Tenenbaum A, Motro M, Fisman EZ, Leor J, Freimark D, Boyko V, Mandelzweig L, Adler Y, Sherer Y, Behar S. Functional class in patients with heart failure is associated with the development of diabetes. Am J Med 2003;114(4):271-5.

17. From AM, Leibson CL, Bursi F, Redfield MM, Weston SA, Jacobsen SJ, Rodeheffer RJ, Roger VL. Diabetes in heart failure: prevalence and impact on outcome in the population. Am J Med 2006;119(7):591-9.

18. Vasan RS, Xanthakis V, Lyass A, Andersson C, Tsao C, Cheng S, Aragam J, Benjamin EJ, Larson MG. Epidemiology of left ventricular systolic dysfunction and heart failure in the Framingham study: an echocardiographic study over 3 decades. JACC Cardiovasc Imaging 2018;11(1):1-11.

19. Kistorp C, Galatius S, Gustafsson F, Faber J, Corell P, Hildebrandt P. Prevalence and characteristics of diabetic patients in a chronic heart failure population. Int J Cardiol 2005;100(2):281-7.

20. Mosterd A, Cost B, Hoes A, De Bruijne M, Deckers J, Hofman A, Grobbee D. The prognosis of heart failure in the general population. The Rotterdam study. Eur Heart J 2001;22(15):1318-27.

21. Thrainsdottir IS, Aspelund T, Thorgeirsson G, Gudnason V, Hardarson T, Malmberg K, Sigurdsson G, Ryden L. The association between glucose abnormalities and heart failure in the population-based Reykjavik study. Diabetes Care 2005;28(3):612-6.

22. Davies M, Hobbs F, Davis R, Kenkre J, Roalfe AK, Hare R, Wosornu D, Lancashire RJ. Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study. Lancet 2001;358(9280):439-44.

23. Amato L, Paolisso G, Cacciatore F, Ferrara N, Ferrara P, Canonico S, Varricchio M, Rengo F. Congestive heart failure predicts the development of non-insulin-dependent diabetes mellitus in the elderly. The Osservatorio Geriatrico Regione Campania Group. Diabetes Metab 1997;23(3):213-8.

24. Gyberg V, De Bacquer D, Kotseva K, De Backer G, Schnell O, Sundvall J, Tuomilehto J, Wood D, Rydén L, Investigators EUROASPIRE IV Investigators. Screening for dysglycaemia in patients with coronary artery disease as reflected by fasting glucose, oral glucose tolerance test, and HbA1c: a report from EUROASPIRE IV-a survey from the European Society of Cardiology. Eur Heart J 2015;36(19):1171-7.

25. Farhan S, Jarai R, Tentzeris I, Kautzky-Willer A, Samaha E, Smetana P, Jakl-Kotauschek G, Wojta J, Huber K. Comparison of HbA1c and oral glucose tolerance test for diagnosis of diabetes in patients with coronary artery disease. Clin Res Cardiol 2012;101(8):625-30.

26. de Mulder M, Oemrawsingh RM, Stam F, Boersma E, Umans VA. Comparison of diagnostic criteria to detect undiagnosed diabetes in hyperglycaemic patients with acute coronary syndrome. Heart 2012;98(1):37-41.

27. Doerr R, Hoffmann U, Otter W, Heinemann L, Hunger-Battefeld W, Kulzer B, Klinge A, Lodwig V, Amann-Zalan I, Sturm D, et al. Oral glucose tolerance test and HbA_{1c} for diagnosis of diabetes in patients undergoing coronary angiography: [corrected] the Silent Diabetes Study. Diabetologia 2011;54(11):2923-30.
28. Kucharska A, Gajewska D, Kiedrowski M, Sińska B, Juszczyk G, Czerw A, Augustynowicz A, Bobiński K, Deptała A, Niegowska J. The impact of individualised nutritional therapy according to DASH diet on blood pressure, body mass, and selected biochemical parameters in overweight/obese patients with primary arterial hypertension: a prospective randomised study. Kardiol Pol 2018;76(1):158-65.
29. Foroozanfard F, Rafiei H, Samimi M, Gilasi HR, Gorjizadeh R, Heidar Z, Asemi Z. The effects of dietary approaches to stop hypertension diet on weight loss, anti-Müllerian hormone and metabolic profiles in women with polycystic ovary syndrome: a randomized clinical trial. Clin Endocrinol (Oxf) 2017;87(1):51-8.
30. Razavi Zade M, Telkabadi MH, Bahmani F, Salehi B, Farshbaf S, Asemi Z. The effects of DASH diet on weight loss and metabolic status in adults with non-alcoholic fatty liver disease: a randomized clinical trial. Liver Int 2016;36(4):563-71.
31. Wong CY, Chaudhry SI, Desai MM, Krumholz HM. Trends in comorbidity, disability, and polypharmacy in heart failure. Am J Med 2011;124(2):136-43.
32. Baena-Díez JM, Peñafiel J, Subirana I, Ramos R, Elosua R, Marín-Ibañez A, Guembe MJ, Rigo F, Tormo-Díaz MJ, Moreno-Iribas C, et al. Risk of cause-specific death in individuals with diabetes: a competing risks analysis. Diabetes Care 2016;39(11):1987-95.

33. Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham study. JAMA 1979;241(19):2035-8.

34. Singh VP, Bali A, Singh N, Jaggi AS. Advanced glycation end products and diabetic complications. Korean J Physiol Pharmacol 2014;18(1):1-14.

35. Inamdar AA, Inamdar AC. Heart failure: diagnosis, management and utilization. J Clin Med 2016;5(7):62.

36. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, et al. 2016 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 J Heart Fail 2016;18(8):891-975.

37. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013;128(16):1810-52.

38. Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, Katz SD, Klapholz M, Moser DK, Rogers JG, et al. HFSA 2010 comprehensive heart failure practice guideline. J Card Fail 2010;16(6):e1-194.

39. Simons JE, Don-Wauchope AC. Evaluation of natriuretic peptide recommendations in heart failure clinical practice guidelines. Clin Biochem 2016;49(1-2):8-15.

40. Tanai E, Frantz S. Pathophysiology of heart failure. Compr Physiol 2011;6(1):187-214.

41. LaCombe P, Tariq MA, Lappin SL. Physiology, Afterload Reduction. Edtion ed. StatPearls. Treasure Island: StatPearls Publishing LLC., 2021.

42. Richards AM. The renin-angiotensin-aldosterone system and the cardiac natriuretic peptides. Heart 1996;76(3 Suppl 3):36-44.

43. White RM. The role of brain natriuretic peptide in systolic heart failure. Dimens Crit Care Nurs 2005;24(4):171-4.

44. Hartupee J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. Nat Rev Cardiol 2017;14(1):30-8.

45. Gjesdal O, Bluemke DA, Lima JA. Cardiac remodeling at the population level—risk factors, screening, and outcomes. Nat Rev Cardiol 2011;8(12):673-85.

46. Konstam MA, Kramer DG, Patel AR, Maron MS, Udelson JE. Left ventricular remodeling in heart failure: current concepts in clinical significance and assessment. JACC Cardiovasc Imaging 2011;4(1):98-108.

47. Watson R, Gibbs C, Lip G. Clinical features and complications. BMJ 2000;320(7229):236-9.

48. Huffman MD, Berry JD, Ning H, Dyer AR, Garside DB, Cai X, Daviglus ML, Lloyd-Jones DM. Lifetime risk for heart failure among white and black Americans: cardiovascular lifetime risk pooling project. J Am Coll Cardiol 2013;61(14):1510-7.

49. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). Am J Cardiol 2008;101(7):1016-22.

50. Barker WH, Mullooly JP, Getchell W. Changing incidence and survival for heart failure in a well-defined older population, 1970-1974 and 1990-1994. Circulation 2006;113(6):799-805.

51. Benjamin E, Muntner P, Alonso A, Bittencourt M, Callaway C, Carson A, Chamberlain A, Chang A, Cheng S, Das S, et al. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation 2019;139(10):e56-528.

52. Russo CA, Elixhauser A. Hospitalizations in the elderly population, 2003: statistical brief #6. In: Healthcare Cost and Utilization Project (HCUP) statistical briefs. Rockville: Agency for Healthcare Research and Quality, 2006.

53. Centers for Medicare & Medicaid Services. Patient Protection and Affordable Care Act Section 3025 Hospital Readmission Reduction Program. Baltimore, MD: Centers for Medicare & Medicaid Services, 2010.

54. Zuckerman RB, Sheingold SH, Orav EJ, Ruhter J, Epstein AM. Readmissions, observation, and the hospital readmissions reduction program. N Engl J Med 2016;374(16):1543-51.

55. Wasfy JH, Zigler CM, Choirat C, Wang Y, Dominici F, Yeh RW. Readmission rates after passage of the hospital readmissions reduction program: a pre-post analysis. Ann Intern Med 2017;166(5):324-31.

56. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2021. Diabetes Care 2021;44(Supplement 1):S15-33.

57. Sacks DB. A1C versus glucose testing: a comparison. Diabetes Care 2011;34(2):518-23.

58. Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. Lancet 2014;383(9922):1068-83.

59. Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward WK, Beard JC, Palmer JP, et al. Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. Diabetes 1993;42(11):1663-72.

60. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37(12):1595-607.

61. Rehman K, Akash MS. Mechanisms of inflammatory responses and development of insulin resistance: how are they interlinked? J Biomed Sci 2016;23(1):87.

62. Ehses JA, Lacraz G, Giroix MH, Schmidlin F, Coulaud J, Kassis N, Irminger JC, Kergoat M, Portha B, Homo-Delarche F, et al. IL-1 antagonism reduces hyperglycemia and tissue inflammation in the type 2 diabetic GK rat. Proc Natl Acad Sci U S A 2009;106(33):13998-4003.

63. Wen H, Gris D, Lei Y, Jha S, Zhang L, Huang MT, Brickey WJ, Ting JP. Fatty acid-induced NLRP3-ASC inflammasome activation interferes with insulin signaling. Nat Immunol 2011;12(5):408-15.

64. Lagathu C, Yvan-Charvet L, Bastard JP, Maachi M, Quignard-Boulange A, Capeau J, Caron M. Long-term treatment with interleukin-1beta induces insulin resistance in murine and human adipocytes. Diabetologia 2006;49(9):2162-73.

65. Nov O, Kohl A, Lewis EC, Bashan N, Dvir I, Ben-Shlomo S, Fishman S, Wueest S, Konrad D, Rudich A. Interleukin-1beta may mediate insulin resistance in liver-derived cells in response to adipocyte inflammation. Endocrinology 2010;151(9):4247-56.

66. Barbarroja N, Lopez-Pedrera C, Garrido-Sanchez L, Mayas MD, Oliva-Olivera W, Bernal-Lopez MR, El Bekay R, Tinahones FJ. Progression from high insulin resistance to

type 2 diabetes does not entail additional visceral adipose tissue inflammation. PLoS One 2012;7(10):e48155.

67. Haffner S, Temprosa M, Crandall J, Fowler S, Goldberg R, Horton E, Marcovina S, Mather K, Orchard T, Ratner R, et al. Intensive lifestyle intervention or metformin on inflammation and coagulation in participants with impaired glucose tolerance. Diabetes 2005;54(5):1566-72.

68. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 1993;259(5091):87-91.

69. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 2007;117(1):175-84.

70. van Haeften TW, Pimenta W, Mitrakou A, Korytkowski M, Jenssen T, Yki-Jarvinen H, Gerich JE. Relative contributions of β-cell function and tissue insulin sensitivity to fasting and postglucose-load glycemia. Metabolism 2000;49(10):1318-25.

71. Skyler JS, Bakris GL, Bonifacio E, Darsow T, Eckel RH, Groop L, Groop P-H, Handelsman Y, Insel RA, Mathieu C, et al. Differentiation of diabetes by pathophysiology, natural history, and prognosis. Diabetes 2017;66(2):241-55.

72. Black SA. Diabetes, diversity, and disparity: what do we do with the evidence? Am J Public Health 2002;92(4):543-8.

73. Piccolo RS, Subramanian S, Pearce N, Florez JC, McKinlay JB. Relative contributions of socioeconomic, local environmental, psychosocial, lifestyle/behavioral, biophysiological, and ancestral factors to racial/ethnic disparities in type 2 diabetes. Diabetes Care 2016;39(7):1208-17.

74. Green LW, Brancati FL, Albright A. Primary prevention of type 2 diabetes: integrative public health and primary care opportunities, challenges and strategies. Fam Pract 2012;29 Suppl 1:i13-23.

75. Schulze MB, Hu FB. Primary prevention of diabetes: what can be done and how much can be prevented? Annu Rev Public Health 2005;26:445-67.

76. Bullard KM, Cowie CC, Lessem SE, Saydah SH, Menke A, Geiss LS, Orchard TJ, Rolka DB, Imperatore G. Prevalence of diagnosed diabetes in adults by diabetes type -United States, 2016. MMWR Morb Mortal Wkly Rep 2018;67(12):359-61.

77. Thierer J, Acosta A, Vainstein N, Sultan M, Francesia A, Marino J, Prado AH, Guglielmone R, Trivi M, Boero L, et al. Relation of left ventricular ejection fraction and functional capacity with metabolism and inflammation in chronic heart failure with reduced ejection fraction (from the MIMICA Study). Am J Cardiol 2010;105(7):977-83.

78. Pfister R, Muller-Ehmsen J, Hagemeister J, Hellmich M, Erdmann E, Schneider CA. NT-pro-BNP predicts worsening renal function in patients with chronic systolic heart failure. Intern Med J 2011;41(6):467-72.

79. Flynn KE, Pina IL, Whellan DJ, Lin L, Blumenthal JA, Ellis SJ, Fine LJ, Howlett JG, Keteyian SJ, Kitzman DW, et al. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301(14):1451-9.

80. Sarma S, Mentz RJ, Kwasny MJ, Fought AJ, Huffman M, Subacius H, Nodari S, Konstam M, Swedberg K, Maggioni AP, et al. Association between diabetes mellitus and post-discharge outcomes in patients hospitalized with heart failure: findings from the EVEREST trial. Eur J Heart Fail 2013;15(2):194-202.

81. Kristensen SL, Jhund PS, Lee MM, Køber L, Solomon SD, Granger CB, Yusuf S, Pfeffer MA, Swedberg K, McMurray JJ, et al. Prevalence of prediabetes and undiagnosed diabetes in patients with HFpEF and HFrEF and associated clinical outcomes. Cardiovasc Drugs Ther 2017;31(5-6):545-9.

82. Egstrup M, Schou M, Gustafsson I, Kistorp CN, Hildebrandt PR, Tuxen CD. Oral glucose tolerance testing in an outpatient heart failure clinic reveals a high proportion of undiagnosed diabetic patients with an adverse prognosis. Eur J Heart Fail 2011;13(3):319-26.

83. Kristensen SL, Preiss D, Jhund PS, Squire I, Cardoso JS, Merkely B, Martinez F, Starling RC, Desai AS, Lefkowitz MP, et al. Risk related to pre-diabetes mellitus and diabetes mellitus in heart failure with reduced ejection fraction: insights from prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial. Circ Heart Fail 2016;9(1):e002560.

84. Targher G, Dauriz M, Tavazzi L, Temporelli PL, Lucci D, Urso R, Lecchi G, Bellanti G, Merlo M, Rossi A, et al. Prognostic impact of in-hospital hyperglycemia in hospitalized patients with acute heart failure: Results of the IN-HF (Italian Network on Heart Failure) Outcome registry. Int J Cardiol 2016;203:587-93.

85. Held C, Gerstein H, Yusuf S, Zhao F, Hilbrich L, Anderson C, Sleight P, Teo K. Glucose levels predict hospitalization for congestive heart failure in patients at high cardiovascular risk. Circulation 2007;115(11):1371-5.

86. MacDonald MR, Petrie MC, Varyani F, Östergren J, Michelson EL, Young JB, Solomon SD, Granger CB, Swedberg K, Yusuf S, et al. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in

Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. Eur Heart J 2008;29(11):1377-85.

87. Gerstein HC, Swedberg K, Carlsson J, McMurray JJ, Michelson EL, Olofsson B, Pfeffer MA, Yusuf S. The hemoglobin A1c level as a progressive risk factor for cardiovascular death, hospitalization for heart failure, or death in patients with chronic heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. Arch Intern Med 2008;168(15):1699-704.

88. Targher G, Dauriz M, Laroche C, Temporelli PL, Hassanein M, Seferovic PM, Drozdz J, Ferrari R, Anker S, Coats A, et al. In-hospital and 1-year mortality associated with diabetes in patients with acute heart failure: results from the ESC-HFA Heart Failure Long-Term Registry. Eur J Heart Fail 2017;19(1):54-65.

89. Kostis JB, Sanders M. The association of heart failure with insulin resistance and the development of type 2 diabetes. Am J Hypertens 2005;18(5 Pt 1):731-7.

90. Paolisso G, De Riu S, Marrazzo G, Verza M, Varricchio M, D'Onofrio F. Insulin resistance and hyperinsulinemia in patients with chronic congestive heart failure. Metabolism 1991;40(9):972-7.

91. Randle P, Garland P, Hales C, Newsholme E. The glucose fatty-acid cycle its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1963;281(7285):785-9.

92. Randle PJ. Regulatory interactions between lipids and carbohydrates: the glucose fatty acid cycle after 35 years. Diabetes Metab Rev 1998;14(4):263-83.

93. Belfort R, Mandarino L, Kashyap S, Wirfel K, Pratipanawatr T, Berria R, Defronzo RA, Cusi K. Dose-response effect of elevated plasma free fatty acid on insulin signaling. Diabetes 2005;54(6):1640-8.

94. Sasaoka T, Wada T, Tsuneki H. Lipid phosphatases as a possible therapeutic target in cases of type 2 diabetes and obesity. Pharmacol Ther 2006;112(3):799-809.

95. Julius U. Influence of plasma free fatty acids on lipoprotein synthesis and diabetic dyslipidemia. Exp Clin Endocrinol Diabetes 2003;111(5):246-50.

96. Van Linthout S, Tschöpe C. Inflammation-cause or consequence of heart failure or both? Curr Heart Fail Rep 2017;14(4):251-65.

97. Wong AK, ALZadjali MA, Choy AMJ, Lang CC. Insulin resistance: a potential new target for therapy in patients with heart failure. Cardiovasc Ther 2008;26(3):203-13.

98. AlZadjali MA, Godfrey V, Khan F, Choy A, Doney AS, Wong AK, Petrie JR, Struthers AD, Lang CC. Insulin resistance is highly prevalent and is associated with reduced exercise tolerance in nondiabetic patients with heart failure. J Am Coll Cardiol 2009;53(9):747-53.

99. Sabelis L, Senden P, Zonderland M, van de Wiel A, Wielders J, Huisveld I, van Haeften T, Mosterd W. Determinants of insulin sensitivity in chronic heart failure. Eur J Heart Fail 2003;5(6):759-65.

100. Wilcox G. Insulin and insulin resistance. Clin Biochem Rev 2005;26(2):19-39.

101. Via M. The malnutrition of obesity: micronutrient deficiencies that promote diabetes. ISRN Endocrinol 2012;2012:103472.

102. Shirani F, Salehi-Abargouei A, Azadbakht L. Effects of Dietary Approaches to Stop Hypertension (DASH) diet on some risk for developing type 2 diabetes: a systematic review and meta-analysis on controlled clinical trials. Nutrition 2013;29(7-8):939-47.

103. Ishihara M, Inoue I, Kawagoe T, Shimatani Y, Kurisu S, Hata T, Nakama Y, Kijima Y, Kagawa E. Is admission hyperglycaemia in non-diabetic patients with acute myocardial infarction a surrogate for previously undiagnosed abnormal glucose tolerance? Eur Heart J 2006;27(20):2413-9.

104. Karnchanasorn R, Huang J, Ou H-Y, Feng W, Chuang L-M, Chiu KC, Samoa R. Comparison of the current diagnostic criterion of HbA1c with fasting and 2-hour plasma glucose concentration. J Diabetes Res 2016;2016:6195494.

105. Swan J, Walton C, Godsland I, Clark A, Coats A, Oliver M. Insulin resistance in chronic heart failure. Eur Heart J 1994;15(11):1528-32.

106. Kim C, Bullard KM, Herman WH, Beckles GL. Association between iron deficiency and A1C levels among adults without diabetes in the National Health and Nutrition Examination Survey, 1999–2006. Diabetes Care 2010;33(4):780-5.

107. Groenveld HF, Januzzi JL, Damman K, van Wijngaarden J, Hillege HL, van Veldhuisen DJ, van der Meer P. Anemia and mortality in heart failure patients: a systematic review and meta-analysis. J Am Coll Cardiol 2008;52(10):818-27.

108. Tang WW, Tong W, Jain A, Francis GS, Harris CM, Young JB. Evaluation and long-term prognosis of new-onset, transient, and persistent anemia in ambulatory patients with chronic heart failure. J Am Coll Cardiol 2008;51(5):569-76.

109. Waldum B, Westheim AS, Sandvik L, Flønæs B, Grundtvig M, Gullestad L, Hole T, Os I. Baseline anemia is not a predictor of all-cause mortality in outpatients with advanced

heart failure or severe renal dysfunction: results from the norwegian heart failure registry. J Am Coll Cardiol 2012;59(4):371-8.

110. Dei Cas A, Khan SS, Butler J, Mentz RJ, Bonow RO, Avogaro A, Tschoepe D, Doehner W, Greene SJ, Senni M, et al. Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure. JACC Heart Fail 2015;3(2):136-45.

111. Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325(5):293-302.

112. Moye LA, Pfeffer MA, Wun CC, Davis BR, Geltman E, Hayes D, Farnham DJ, Randall OS, Dinh H, Arnold JM, et al. Uniformity of captopril benefit in the SAVE Study: subgroup analysis. Survival and Ventricular Enlargement Study. Eur Heart J 1994;15 Suppl B:2-8; discussion 26-30.

113. Young JB, Dunlap ME, Pfeffer MA, Probstfield JL, Cohen-Solal A, Dietz R, Granger CB, Hradec J, Kuch J, McKelvie RS, et al. Mortality and morbidity reduction with Candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials. Circulation 2004;110(17):2618-26.

114. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345(23):1667-75.

115. Shekelle PG, Rich MW, Morton SC, Atkinson CS, Tu W, Maglione M, Rhodes S, Barrett M, Fonarow GC, Greenberg B, et al. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction

according to race, gender, and diabetic status: a meta-analysis of major clinical trials. J Am Coll Cardiol 2003;41(9):1529-38.

116. Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, Riegger GA, Malbecq W, Smith RD, Guptha S, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. Lancet 2009;374(9704):1840-8.

117. Maggioni AP, Greene SJ, Fonarow GC, Bohm M, Zannad F, Solomon SD, Lewis EF, Baschiera F, Hua TA, Gimpelewicz CR, et al. Effect of aliskiren on post-discharge outcomes among diabetic and non-diabetic patients hospitalized for heart failure: insights from the ASTRONAUT trial. Eur Heart J 2013;34(40):3117-27.

118. Gheorghiade M, Bohm M, Greene SJ, Fonarow GC, Lewis EF, Zannad F, Solomon SD, Baschiera F, Botha J, Hua TA, et al. Effect of aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure: the ASTRONAUT randomized trial. JAMA 2013;309(11):1125-35.

119. Zhou MS, Schulman IH, Jaimes EA, Raij L. Thiazide diuretics, endothelial function, and vascular oxidative stress. J Hypertens 2008;26(3):494-500.

120. Lithell HO. Effect of antihypertensive drugs on insulin, glucose, and lipid metabolism. Diabetes Care 1991;14(3):203-9.

121. Ferrari P, Rosman J, Weidmann P. Antihypertensive agents, serum lipoproteins and glucose metabolism. Am J Cardiol 1991;67(10):26b-35b.

122. Eriksson JW, Jansson PA, Carlberg B, Hagg A, Kurland L, Svensson MK, Ahlstrom H, Strom C, Lonn L, Ojbrandt K, et al. Hydrochlorothiazide, but not candesartan, aggravates insulin resistance and causes visceral and hepatic fat accumulation: the mechanisms for

the diabetes preventing effect of candesartan (MEDICA) Study. Hypertension 2008;52(6):1030-7.

123. Grassi G, Seravalle G, Dell'Oro R, Trevano FQ, Bombelli M, Scopelliti F, Facchini A, Mancia G. Comparative effects of candesartan and hydrochlorothiazide on blood pressure, insulin sensitivity, and sympathetic drive in obese hypertensive individuals: results of the CROSS study. J Hypertens 2003;21(9):1761-9.

124. Burnier M, Brunner HR. Neurohormonal consequences of diuretics in different cardiovascular syndromes. Eur Heart J 1992;13 Suppl G:28-33.

125. Smooke S, Horwich TB, Fonarow GC. Insulin-treated diabetes is associated with a marked increase in mortality in patients with advanced heart failure. Am Heart J 2005;149(1):168-74.

126. Damluji AA, Cohen ER, Moscucci M, Myerburg RJ, Cohen MG, Brooks MM, Rich MW, Forman DE. Insulin provision therapy and mortality in older adults with diabetes mellitus and stable ischemic heart disease: Insights from BARI-2D trial. Int J Cardiol 2017;241:35-40.

127. Aguilar D, Bozkurt B, Pritchett A, Petersen NJ, Deswal A. The impact of thiazolidinedione use on outcomes in ambulatory patients with diabetes mellitus and heart failure. J Am Coll Cardiol 2007;50(1):32-6.

128. Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, Le Winter M, Porte D, Semenkovich CF, Smith S, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. Circulation 2003;108(23):2941-8.

129. Lipscombe LL, Gomes T, Levesque LE, Hux JE, Juurlink DN, Alter DA. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. JAMA 2007;298(22):2634-43.

130. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. Lancet 2007;370(9593):1129-36.

131. Monami M, Dicembrini I, Mannucci E. Dipeptidyl peptidase-4 inhibitors and heart failure: a meta-analysis of randomized clinical trials. Nutr Metab Cardiovasc Dis 2014;24(7):689-97.

132. Savarese G, Perrone-Filardi P, D'Amore C, Vitale C, Trimarco B, Pani L, Rosano GM. Cardiovascular effects of dipeptidyl peptidase-4 inhibitors in diabetic patients: a meta-analysis. Int J Cardiol 2015;181:239-44.

133. Sato A, Yoshihisa A, Kanno Y, Takiguchi M, Miura S, Shimizu T, Nakamura Y, Yamauchi H, Owada T, Sato T, et al. Associations of dipeptidyl peptidase-4 inhibitors with mortality in hospitalized heart failure patients with diabetes mellitus. ESC Heart Fail 2016;3(2):77-85.

134. Filion KB, Azoulay L, Platt RW, Dahl M, Dormuth CR, Clemens KK, Hu N, Paterson JM, Targownik L, Turin TC, et al. A multicenter observational study of incretin-based drugs and heart failure. N Engl J Med 2016;374(12):1145-54.

135. Margulies KB, Hernandez AF, Redfield MM, Givertz MM, Oliveira GH, Cole R, Mann DL, Whellan DJ, Kiernan MS, Felker GM, et al. Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: a randomized clinical trial. JAMA 2016;316(5):500-8.

136. Jorsal A, Kistorp C, Holmager P, Tougaard RS, Nielsen R, Hanselmann A, Nilsson B, Moller JE, Hjort J, Rasmussen J, et al. Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE)-a multicentre, double-blind, randomised, placebo-controlled trial. Eur J Heart Fail 2017;19(1):69-77.

137. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373(22):2117-28.

138. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. Eur Heart J 2016;37(19):1526-34.

139. Maejima Y. SGLT2 inhibitors play a salutary role in heart failure via modulation of the mitochondrial function. Front Cardiovasc Med 2020;6:186.

140. Ferrannini E, Mark M, Mayoux E. CV Protection in the EMPA-REG OUTCOME trial: a "Thrifty Substrate" hypothesis. Diabetes Care 2016;39(7):1108-14.

141. Marx N, McGuire DK. Sodium-glucose cotransporter-2 inhibition for the reduction of cardiovascular events in high-risk patients with diabetes mellitus. Eur Heart J 2016;37(42):3192-200.

142. Aquilani R, Opasich C, Verri M, Boschi F, Febo O, Pasini E, Pastoris O. Is nutritional intake adequate in chronic heart failure patients? J Am Coll Cardiol 2003;42(7):1218-23.

143. Rahman A, Jafry S, Jeejeebhoy K, Nagpal AD, Pisani B, Agarwala R. Malnutrition and cachexia in heart failure. JPEN J Parenter Enteral Nutr 2016;40(4):475-86.

144. Landi F, Calvani R, Tosato M, Martone AM, Ortolani E, Savera G, Sisto A, Marzetti E. Anorexia of aging: risk factors, consequences, and potential treatments. Nutrients 2016;8(2):69.

145. Sciatti E, Lombardi C, Ravera A, Vizzardi E, Bonadei I, Carubelli V, Gorga E, Metra M. Nutritional deficiency in patients with heart failure. Nutrients 2016;8(7):442.

146. McKeag NA, McKinley MC, Woodside JV, Harbinson MT, McKeown PP. The role of micronutrients in heart failure. J Acad Nutr Diet 2012;112(6):870-86.

147. Lemon SC, Olendzki B, Magner R, Li W, Culver AL, Ockene I, Goldberg RJ. The dietary quality of persons with heart failure in NHANES 1999–2006. J Gen Intern Med 2010;25(2):135-40.

148. Arcand J, Floras V, Ahmed M, Al-Hesayen A, Ivanov J, Allard JP, Newton GE. Nutritional inadequacies in patients with stable heart failure. J Am Diet Assoc 2009;109(11):1909-13.

149. Dunn SP, Bleske B, Dorsch M, Macaulay T, Van Tassell B, Vardeny O. Nutrition and heart failure: impact of drug therapies and management strategies. Nutr Clin Pract 2009;24(1):60-75.

150. Abu-Sawwa R, Dunbar SB, Quyyumi AA, Sattler EL. Nutrition intervention in heart failure: should consumption of the DASH eating pattern be recommended to improve outcomes? Heart Fail Rev 2019;24(4):565-73.

151. Bonilla-Palomas J, Gámez-López A, Moreno-Conde M, López-Ibáñez C, Anguita-Sánchez M, Castillo-Domínguez J, López López J, Gallego de la Sacristana A. La desnutrición detectada durante la hospitalización incrementa el riesgo de reingreso en pacientes con insuficiencia cardiaca. Rev Esp Cardiol 2011;64(Supl 3):116.

152. Bonilla-Palomas JL, Gámez-López AL, Moreno-Conde M, López-Ibáñez MC, Castellano-García P, Ráez-Ruiz CJ, Ruíz-Quirós R, Ramiro-Ortega E. Influencia de la desnutrición sobre la mortalidad a largo plazo en pacientes ambulatorios con insuficiencia cardiaca crónica. Nutrición Hospitalaria 2017;34(6):1382-9.

153. Abshire M, Xu J, Baptiste D, Almansa JR, Xu J, Cummings A, Andrews MJ, Himmelfarb CD. Nutritional interventions in heart failure: a systematic review of the literature. J Card Fail 2015;21(12):989-99.

154. DiNicolantonio JJ, Chatterjee S, O'Keefe JH. Dietary salt restriction in heart failure: where is the evidence? Prog Cardiovasc Dis 2016;58(4):401-6.

155. Frediani JK, Reilly CM, Higgins M, Clark PC, Gary RA, Dunbar SB. Quality and adequacy of dietary intake in a southern urban heart failure population. J Cardiovasc Nurs 2013;28(2):119-28.

156. Jefferson K, Ahmed M, Choleva M, Mak S, Allard JP, Newton GE, Arcand J. Effect of a sodium-restricted diet on intake of other nutrients in heart failure: implications for research and clinical practice. J Card Fail 2015;21(12):959-62.

157. Evert AB, Boucher JL, Cypress M, Dunbar SA, Franz MJ, Mayer-Davis EJ, Neumiller JJ, Nwankwo R, Verdi CL, Urbanski P, et al. Nutrition therapy recommendations for the management of adults with diabetes. Diabetes Care 2014;36(11):3821-42.

158. Davies MJ, D’Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, Rossing P, Tsapas A, Wexler DJ, Buse JB. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2018;61(12):2461-98.

159. Early KB, Stanley K. Position of the Academy of Nutrition and Dietetics: the role of medical nutrition therapy and registered dietitian nutritionists in the prevention and treatment of prediabetes and type 2 diabetes. J Acad Nutr Diet 2018;118(2):343-53.

160. American Diabetes Association. 5. Lifestyle management: standards of medical care in diabetes-2019. Diabetes Care 2019;42(Suppl 1):S46-60.

161. MacLeod J, Franz MJ, Handu D, Gradwell E, Brown C, Evert A, Reppert A, Robinson M. Academy of Nutrition and Dietetics nutrition practice guideline for type 1 and type 2 diabetes in adults: nutrition intervention evidence reviews and recommendations. J Acad Nutr Diet 2017;117(10):1637-58.

162. Schwingshackl L, Schwedhelm C, Hoffmann G, Lampousi A-M, Knüppel S, Iqbal K, Bechthold A, Schlesinger S, Boeing H. Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr 2017;105(6):1462-73.

163. Esposito K, Maiorino MI, Ciotola M, Di Palo C, Scognamiglio P, Gicchino M, Petrizzo M, Saccomanno F, Beneduce F, Ceriello A, et al. Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial. Ann Intern Med 2009;151(5):306-14.

164. Boucher JL. Mediterranean eating pattern. Diabetes Spectr 2017;30(2):72-6.

165. Cespedes EM, Hu FB, Tinker L, Rosner B, Redline S, Garcia L, Hingle M, Van Horn L, Howard BV, Levitan EB, et al. Multiple healthful dietary patterns and type 2 diabetes in the Women's Health Initiative. Am J Epidemiol 2016;183(7):622-33.

166. Ley SH, Hamdy O, Mohan V, Hu FB. Prevention and management of type 2 diabetes: dietary components and nutritional strategies. Lancet 2014;383(9933):1999-2007.

167. Campbell AP. DASH eating plan: an eating pattern for diabetes management. Diabetes Spectr 2017;30(2):76-81.

168. Rinaldi S, Campbell EE, Fournier J, O'Connor C, Madill J. A comprehensive review of the literature supporting recommendations from the Canadian Diabetes Association for the use of a plant-based diet for management of type 2 diabetes. Can J Diabetes 2016;40(5):471-7.

169. Pawlak R. Vegetarian diets in the prevention and management of diabetes and its complications. Diabetes Spectr 2017;30(2):82-8.

170. Saslow LR, Daubenmier JJ, Moskowitz JT, Kim S, Murphy EJ, Phinney SD, Ploutz-Snyder R, Goldman V, Cox RM, Mason AE, et al. Twelve-month outcomes of a randomized trial of a moderate-carbohydrate versus very low-carbohydrate diet in overweight adults with type 2 diabetes mellitus or prediabetes. Nutr Diabetes 2017;7(12):304.

171. Hallberg SJ, McKenzie AL, Williams PT, Bhanpuri NH, Peters AL, Campbell WW, Hazbun TL, Volk BM, McCarter JP, Phinney SD, et al. Effectiveness and safety of a novel care model for the management of type 2 diabetes at 1 year: an open-label, non-randomized, controlled study. Diabetes Ther 2018;9(2):583-612.

172. Sainsbury E, Kizirian NV, Partridge SR, Gill T, Colagiuri S, Gibson AA. Effect of dietary carbohydrate restriction on glycemic control in adults with diabetes: a systematic review and meta-analysis. Diabetes Res Clin Pract 2018;139:239-52.

173. Blau JE, Tella SH, Taylor SI, Rother KI. Ketoacidosis associated with SGLT2 inhibitor treatment: analysis of FAERS data. Diabetes Metab Res Rev 2017;33(8):e2924.

174. Bowen ME, Cavanaugh KL, Wolff K, Davis D, Gregory RP, Shintani A, Eden S, Wallston K, Elasy T, Rothman RL. The diabetes nutrition education study randomized controlled trial: a comparative effectiveness study of approaches to nutrition in diabetes self-management education. Patient Educ Couns 2016;99(8):1368-76.

175. Eckel RH, Kahn SE, Ferrannini E, Goldfine AB, Nathan DM, Schwartz MW, Smith RJ, Smith SR. Obesity and type 2 diabetes: what can be unified and what needs to be individualized? J Clin Endocrinol Metab 2011;96(6):1654-63.

176. Bagdade JD, Bierman EL, Porte D. The significance of basal insulin levels in the evaluation of the insulin response to glucose in diabetic and nondiabetic subjects. J Clin Invest 1967;46(10):1549-57.

177. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. β-cell deficit and increased β-cell apoptosis in humans with type 2 diabetes. Diabetes 2003;52(1):102-10.

178. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 2006;444(7121):840.

179. Hamdy O, Mottalib A, Morsi A, El-Sayed N, Goebel-Fabbri A, Arathuzik G, Shahar J, Kirpitch A, Zrebiec J. Long-term effect of intensive lifestyle intervention on cardiovascular risk factors in patients with diabetes in real-world clinical practice: a 5-year longitudinal study. BMJ Open Diabetes Res Care 2017;5(1):e000259.

180. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, Peters C, Zhyzhneuskaya S, Al-Mrabeh A, Hollingsworth KG, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet 2018;391(10120):541-51.

181. Mottalib A, Salsberg V, Mohd-Yusof B-N, Mohamed W, Carolan P, Pober DM, Mitri J, Hamdy O. Effects of nutrition therapy on HbA1c and cardiovascular disease risk factors in overweight and obese patients with type 2 diabetes. Nutr J 2018;17(1):42.

182. Estruch R, Ros E, Salas-Salvadó J, Covas M, Corella D, Arós F. PREDIMED study investigators. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013;368:1279-90.

183. Seferovic PM, Ponikowski P, Anker SD, Bauersachs J, Chioncel O, Cleland JG, de Boer RA, Drexel H, Ben Gal T, Hill L, et al. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2019;21(10):1169-86.

184. Leung CC. Current role of the CardioMEMS device for management of patients with heart failure. Curr Cardiol Rep 2019;21(9):98.

185. Narumi T, Arimoto T, Funayama A, Kadowaki S, Otaki Y, Nishiyama S, Takahashi H, Shishido T, Miyashita T, Miyamoto T, et al. The prognostic importance of objective nutritional indexes in patients with chronic heart failure. J Cardiol 2013;62(5):307-13.

186. Agra Bermejo RM, Gonzalez Ferreiro R, Varela Roman A, Gomez Otero I, Kreidieh O, Conde Sabaris P, Rodriguez-Manero M, Moure Gonzalez M, Seoane Blanco A, Virgos Lamela A, et al. Nutritional status is related to heart failure severity and hospital readmissions in acute heart failure. Int J Cardiol 2017;230:108-14.

187. Cheng YL, Sung SH, Cheng HM, Hsu PF, Guo CY, Yu WC, Chen CH. Prognostic Nutritional Index and the risk of mortality in patients with acute heart failure. J Am Heart Assoc 2017;6(6):e004876.

188. Yancy CW JM, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013(128):e240–e327.

189. Atherton JJ, Sindone A, De Pasquale CG, Driscoll A, MacDonald PS, Hopper I, Kistler PM, Briffa T, Wong J, Abhayaratna W, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: guidelines for the prevention, detection, and management of heart failure in Australia 2018. Heart Lung Circ 2018;27(10):1123-208.

190. Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, Giannetti N, Grzeslo A, Hamilton PG, Heckman GA, et al. 2017 comprehensive update of the Canadian Cardiovascular Society guidelines for the management of heart failure. Can J Cardiol 2017;33(11):1342-433.

191. Scottish Intercollegiate Guidelines Network (SIGN). Management of chronic heart failure. Internet: https://www.sign.ac.uk/assets/sign147.pdf (accessed 1 October 2021).

192. Schwengel RH, Gottlieb SS, Fisher ML. Protein-energy malnutrition in patients with ischemic and nonischemic dilated cardiomyopathy and congestive heart failure. Am J Cardiol 1994;73(12):908-10.

193. Vest AR, Chan M, Deswal A, Givertz MM, Lekavich C, Lennie T, Litwin SE, Parsly L, Rodgers JE, Rich MW, et al. Nutrition, obesity, and cachexia in patients with heart failure: a consensus statement from the Heart Failure Society of America scientific statements committee. J Card Fail 2019;25(5):380-400.

194. Cvetinovic N, Loncar G, Isakovic AM, von Haehling S, Doehner W, Lainscak M, Farkas J. Micronutrient depletion in heart failure: common, clinically relevant and treatable. Int J Mol Sci 2019;20(22):5627.

195. McKeag NA, McKinley MC, Harbinson MT, McGinty A, Neville CE, Woodside JV, McKeown PP. Dietary micronutrient intake and micronutrient status in patients with chronic stable heart failure: an observational study. J Cardiovasc Nurs 2017;32(2):148-55.

196. Montgomery SC, Streit SM, Beebe ML, Maxwell PJt. Micronutrient needs of the elderly. Nutr Clin Pract 2014;29(4):435-44.

197. Zittermann A, Schleithoff SS, Tenderich G, Berthold HK, Körfer R, Stehle P. Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure? J Am Coll Cardiol 2003;41(1):105-12.

198. Keith ME, Walsh NA, Darling PB, Hanninen SA, Thirugnanam S, Leong-Poi H, Barr A, Sole MJ. B-vitamin deficiency in hospitalized patients with heart failure. J Am Diet Assoc 2009;109(8):1406-10.

199. de Lorgeril M, Salen P, Accominotti M, Cadau M, Steghens JP, Boucher F, de Leiris J. Dietary and blood antioxidants in patients with chronic heart failure. Insights into the potential importance of selenium in heart failure. Eur J Heart Fail 2001;3(6):661-9.

200. Demirbag R, Yilmaz R, Erel O, Gultekin U, Asci D, Elbasan Z. The relationship between potency of oxidative stress and severity of dilated cardiomyopathy. Can J Cardiol 2005;21(10):851-5.

201. Topuzoglu G, Erbay AR, Karul AB, Yensel N. Concentrations of copper, zinc, and magnesium in sera from patients with idiopathic dilated cardiomyopathy. Biol Trace Elem Res 2003;95(1):11-7.

202. Shetty PM, Hauptman PJ, Landfried LK, Patel K, Weiss EP. Micronutrient deficiencies in patients with heart failure: relationships with body mass index and age. J Card Fail 2015;21(12):968-72.

203. Lennie TA, Andreae C, Rayens MK, Song EK, Dunbar SB, Pressler SJ, Heo S, Kim J, Moser DK. Micronutrient deficiency independently predicts time to event in patients with heart failure. J Am Heart Assoc 2018;7(17):e007251.

204. Karadima V, Kraniotou C, Bellos G, Tsangaris GT. Drug-micronutrient interactions: food for thought and thought for action. EPMA J 2016;7(1):10.

205. Prescott JD, Drake VJ, Stevens JF. Medications and micronutrients: identifying clinically relevant interactions and addressing nutritional needs. J Pharm Technol 2018;34(5):216-30.

206. Jacobsson A, Pihl-Lindgren E, Fridlund B. Malnutrition in patients suffering from chronic heart failure; the nurse's care. Eur J Heart Fail 2001;3(4):449-56.

207. Tsuruoka S, Wakaumi M, Araki N, Ioka T, Sugimoto K, Fujimura A. Comparative study of taste disturbance by losartan and perindopril in healthy volunteers. J Clin Pharmacol 2005;45(11):1319-23.

208. Tsuruoka S, Wakaumi M, Nishiki K, Araki N, Harada K, Sugimoto K, Fujimura A. Subclinical alteration of taste sensitivity induced by candesartan in healthy subjects. Br J Clin Pharmacol 2004;57(6):807-12.

209. Garrido-Maraver J, Cordero MD, Oropesa-Avila M, Fernandez Vega A, de la Mata M, Delgado Pavon A, de Miguel M, Perez Calero C, Villanueva Paz M, Cotan D, et al. Coenzyme Q10 therapy. Mol Syndromol 2014;5(3-4):187-97.

210. Sica DA. Antihypertensive therapy and its effects on potassium homeostasis. J Clin Hypertens (Greenwich) 2006;8(1):67-73.

211. Bowling CB, Pitt B, Ahmed MI, Aban IB, Sanders PW, Mujib M, Campbell RC, Love TE, Aronow WS, Allman RM, et al. Hypokalemia and outcomes in patients with chronic heart failure and chronic kidney disease: findings from propensity-matched studies. Circ Heart Fail 2010;3(2):253-60.

212. Akashi YJ, Springer J, Anker SD. Cachexia in chronic heart failure: prognostic implications and novel therapeutic approaches. Curr Heart Fail Rep 2005;2(4):198-203.

213. Aune D, Sen A, Norat T, Janszky I, Romundstad P, Tonstad S, Vatten LJ. Body mass index, abdominal fatness, and heart failure incidence and mortality: a systematic review and dose-response meta-analysis of prospective studies. Circulation 2016;133(7):639-49.

214. Del Gobbo LC, Kalantarian S, Imamura F, Lemaitre R, Siscovick DS, Psaty BM, Mozaffarian D. Contribution of major lifestyle risk factors for incident heart failure in older adults: the Cardiovascular Health study. JACC Heart Fail 2015;3(7):520-8.

215. Simonenko M. Obesity paradox in heart failure: a matter of debate. Eur J Prev Cardiol 2019;26(16):1748-50.

216. Ebong IA, Goff DC, Jr., Rodriguez CJ, Chen H, Bertoni AG. Mechanisms of heart failure in obesity. Obes Res Clin Pract 2014;8(6):e540-8.

217. Lin GM, Li YH, Yin WH, Wu YW, Chu PH, Wu CC, Hsu CH, Wen MS, Voon WC, Wang CC, et al. The obesity-mortality paradox in patients with heart failure in Taiwan

and a collaborative meta-analysis for East Asian patients. Am J Cardiol 2016;118(7):1011-8.

218. Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. Am Heart J 2008;156(1):13-22.

219. Padwal R, McAlister FA, McMurray JJ, Cowie MR, Rich M, Pocock S, Swedberg K, Maggioni A, Gamble G, Ariti C, et al. The obesity paradox in heart failure patients with preserved versus reduced ejection fraction: a meta-analysis of individual patient data. Int J Obes (Lond) 2014;38(8):1110-4.

220. Alpert MA. Obesity cardiomyopathy: pathophysiology and evolution of the clinical syndrome. Am J Med Sci 2001;321(4):225-36.

221. Kasper EK, Hruban RH, Baughman KL. Cardiomyopathy of obesity: a clinicopathologic evaluation of 43 obese patients with heart failure. Am J Cardiol 1992;70(9):921-4.

222. Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. JACC Heart Fail 2013;1(2):93-102.

223. Adamopoulos C, Meyer P, Desai RV, Karatzidou K, Ovalle F, White M, Aban I, Love TE, Deedwania P, Anker SD, et al. Absence of obesity paradox in patients with chronic heart failure and diabetes mellitus: a propensity-matched study. Eur J Heart Fail 2011;13(2):200-6.

224. Mahajan R, Stokes M, Elliott A, Munawar DA, Khokhar KB, Thiyagarajah A, Hendriks J, Linz D, Gallagher C, Kaye D, et al. Complex interaction of obesity, intentional weight loss and heart failure: a systematic review and meta-analysis. Heart 2020;106(1):58-68.

225. He FJ, Tan M, Ma Y, MacGregor GA. Salt reduction to prevent hypertension and cardiovascular disease: JACC state-of-the-art review. J Am Coll Cardiol 2020;75(6):632-47.

226. Jones DW. Dietary sodium and blood pressure. Hypertension 2004;43(5):932-5.

227. Seth S, Ramakrishnan S, Parekh N, Karthikeyan G, Singh S, Sharma G. Heart failure guidelines for India: update 2017. J Pract Cardiovasc Sci 2017;3(3):133.

228. National Institute for Health and Clinical Excellence, Royal College of Physicians. Chronic heart failure: national clinical guidelines for the diagnosis and management in primary and secondary care. Internet: https://www.nice.org.uk/guidance/ng106/resources/chronic-heart-failure-in-adults-diagnosis-and-management-pdf-66141541311685 (accessed 1 October 2021).

229. Kuehneman T, Gregory M, de Waal D, Davidson P, Frickel R, King C, Gradwell E, Handu D. Academy of Nutrition and Dietetics evidence-based practice guideline for the management of heart failure in adults. J Acad Nutr Diet 2018;118(12):2331-45.

230. Mahtani KR, Heneghan C, Onakpoya I, Tierney S, Aronson JK, Roberts N, Hobbs FDR, Nunan D. Reduced salt intake for heart failure: a systematic review. JAMA Intern Med 2018;178(12):1693-700.

231. Fabricio CG, Tanaka DM, Souza Gentil JR, Ferreira Amato CA, Marques F, Schwartzmann PV, Schmidt A, Simoes MV. A normal sodium diet preserves serum sodium levels during treatment of acute decompensated heart failure: a prospective, blind and randomized trial. Clin Nutr ESPEN 2019;32:145-52.

232. Aliti GB, Rabelo ER, Clausell N, Rohde LE, Biolo A, Beck-da-Silva L. Aggressive fluid and sodium restriction in acute decompensated heart failure: a randomized clinical trial. JAMA Intern Med 2013;173(12):1058-64.

233. Khan MS, Jones DW, Butler J. Salt, no salt, or less salt for patients with heart failure? Am J Med 2020;133(1):32-8.

234. Paterna S, Parrinello G, Cannizzaro S, Fasullo S, Torres D, Sarullo FM, Di Pasquale P. Medium term effects of different dosage of diuretic, sodium, and fluid administration on neurohormonal and clinical outcome in patients with recently compensated heart failure. Am J Cardiol 2009;103(1):93-102.

235. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to update the 2001 guidelines for the evaluation and management of heart failure): Developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation 2005;112(12):e154-235.

236. Grossniklaus DA, O’Brien MC, Clark PC, Dunbar SB. Nutrient intake in heart failure patients. J Cardiovasc Nurs 2008;23(4):357-63.

237. Murtaugh MA, Beasley JM, Appel LJ, Guenther PM, McFadden M, Greene T, Tooze JA. Relationship of sodium intake and blood pressure varies with energy intake: secondary analysis of the DASH (Dietary Approaches to Stop Hypertension)-Sodium trial. Hypertension 2018;71(5):858-65.

238. Marsh K, Zeuschner C, Saunders A. Health implications of a vegetarian diet: a review. Am J Lifestyle Med 2012;6(3):250-67.

239. Yokoyama Y, Nishimura K, Barnard ND, Takegami M, Watanabe M, Sekikawa A, Okamura T, Miyamoto Y. Vegetarian diets and blood pressure: a meta-analysis. JAMA Intern Med 2014;174(4):577-87.

240. Dinu M, Abbate R, Gensini GF, Casini A, Sofi F. Vegetarian, vegan diets and multiple health outcomes: a systematic review with meta-analysis of observational studies. Crit Rev Food Sci Nutr 2017;57(17):3640-9.

241. Tuso P, Stoll SR, Li WW. A plant-based diet, atherogenesis, and coronary artery disease prevention. Perm J 2015;19(1):62-7.

242. Lara KM, Levitan EB, Gutierrez OM, Shikany JM, Safford MM, Judd SE, Rosenson RS. Dietary patterns and incident heart failure in US adults without known coronary disease. J Am Coll Cardiol 2019;73(16):2036-45.

243. Rautiainen S, Levitan EB, Mittleman MA, Wolk A. Fruit and vegetable intake and rate of heart failure: a population-based prospective cohort of women. Eur J Heart Fail 2015;17(1):20-6.

244. Chainani-Wu N, Weidner G, Purnell DM, Frenda S, Merritt-Worden T, Kemp C, Kersh E, Ornish D. Relation of B-type natriuretic peptide levels to body mass index after comprehensive lifestyle changes. Am J Cardiol 2010;105(11):1570-6.

245. Pischke CR, Weidner G, Elliott-Eller M, Ornish D. Lifestyle changes and clinical profile in coronary heart disease patients with an ejection fraction of < or = 40% or > 40% in the Multicenter Lifestyle Demonstration project. Eur J Heart Fail 2007;9(9):928-34.

246. Ornish D, Scherwitz LW, Doody RS, Kesten D, McLanahan SM, Brown SE, DePuey E, Sonnemaker R, Haynes C, Lester J, et al. Effects of stress management training and dietary changes in treating ischemic heart disease. JAMA 1983;249(1):54-9.

247. Pischke CR, Elliott-Eller M, Li M, Mendell N, Ornish D, Weidner G. Clinical events in coronary heart disease patients with an ejection fraction of 40% or less: 3-year follow-up results. J Cardiovasc Nurs 2010;25(5):E8-15.

248. Choi EY, Allen K, McDonnough M, Massera D, Ostfeld RJ. A plant-based diet and heart failure: case report and literature review. J Geriatr Cardiol 2017;14(5):375-8.

249. Allen KE, Gumber D, Ostfeld RJ. Heart failure and a plant-based diet. A case-report and literature review. Front Nutr 2019;6:82.

250. Najjar RS, Montgomery BD. A defined, plant-based diet as a potential therapeutic approach in the treatment of heart failure: A clinical case series. Complement Ther Med 2019;45:211-4.

251. U.S. Department of Health and Human Services, National Heart Lung and Blood Institute, National Institutes of Health. Description of the DASH eating plan. Internet: https://www.nhlbi.nih.gov/health/health-topics/topics/dash (accessed 1 October 2021).

252. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, et al. A clinical trial of the effects of dietary patterns on blood pressure. N Engl J Med 1997;336(16):1117-24.

253. Chiavaroli L, Viguiliouk E, Nishi SK, Blanco Mejia S, Rahelić D, Kahleová H, Salas-Salvadó J, Kendall CW, Sievenpiper JL. DASH dietary pattern and cardiometabolic outcomes: an umbrella review of systematic reviews and meta-analyses. Nutrients 2019;11(2):338.

254. Soltani S, Arablou T, Jayedi A, Salehi-Abargouei A. Adherence to the dietary approaches to stop hypertension (DASH) diet in relation to all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis of prospective cohort studies. Nutr J 2020;19:37.

255. Siervo M, Lara J, Chowdhury S, Ashor A, Oggioni C, Mathers JC. Effects of the Dietary Approach to Stop Hypertension (DASH) diet on cardiovascular risk factors: a systematic review and meta-analysis. Br J Nutr 2015;113(1):1-15.

256. Neale E, Batterham M, Tapsell LC. Consumption of a healthy dietary pattern results in significant reductions in C-reactive protein levels in adults: a meta-analysis. Nutr Res 2016;36(5):391-401.

257. Levitan EB, Lewis CE, Tinker LF, Eaton CB, Ahmed A, Manson JE, Snetselaar LG, Martin LW, Trevisan M, Howard BV. Mediterranean and DASH diet scores and mortality in women with heart failure: The Women's Health Initiative. Circ Heart Fail 2013;6(6):1116-23.

258. Hummel SL, Seymour EM, Brook RD, Kolias TJ, Sheth SS, Rosenblum HR, Wells JM, Weder AB. Low-sodium dietary approaches to stop hypertension diet reduces blood pressure, arterial stiffness, and oxidative stress in hypertensive heart failure with preserved ejection fraction. Hypertension 2012;60(5):1200-6.

259. Hummel SL, Seymour EM, Brook RD, Sheth SS, Ghosh E, Zhu S, Weder AB, Kovács SJ, Kolias TJ. Low-sodium DASH diet improves diastolic function and ventricular-arterial coupling in hypertensive heart failure with preserved ejection fraction clinical perspective. Circ Heart Fail 2013;6(6):1165-71.

260. Mathew AV, Seymour EM, Byun J, Pennathur S, Hummel SL. Altered metabolic profile with sodium-restricted dietary approaches to stop hypertension diet in hypertensive heart failure with preserved ejection fraction. J Card Fail 2015;21(12):963-7.

261. Rifai L, Pisano C, Hayden J, Sulo S, Silver MA. Impact of the DASH diet on endothelial function, exercise capacity, and quality of life in patients with heart failure. Proc (Bayl Univ Med Cent) 2015;28(2):151-6.

262. Hummel SL, Karmally W, Gillespie BW, Helmke S, Teruya S, Wells J, Trumble E, Jimenez O, Marolt C, Wessler JD. Home-delivered meals postdischarge from heart failure hospitalization: the GOURMET-HF pilot study. Circ Heart Fail 2018;11(8):e004886.

263. Estruch R, Ros E, Salas-Salvadó J, Covas M-I, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013;368(14):1279-90.

264. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation 1999;99(6):779-85.

265. Fitó M, Estruch R, Salas-Salvadó J, Martínez-Gonzalez MA, Arós F, Vila J, Corella D, Díaz O, Sáez G, De La Torre R, et al. Effect of the Mediterranean diet on heart failure biomarkers: a randomized sample from the PREDIMED trial. Eur J Heart Fail 2014;16(5):543-50.

266. Habaybeh D, de Moraes MB, Slee A, Avgerinou C. Nutritional interventions for heart failure patients who are malnourished or at risk of malnutrition or cachexia: a systematic review and meta-analysis. Heart Fail Rev 2020;26(5):1103-18.

267. U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute. Nutrition and diet in heart failure management. Internet: https://www.nhlbi.nih.gov/events/2013/nutrition-and-diet-heart-failure-management (accessed 1 October 2021).

268. U.S. Department of Health and Human Services, National Institute of Health, National Center for Advancing Translational Sciences. About the CTSA program. Internet: https://ncats.nih.gov/ctsa/about (accessed 1 October 2021).

269. American Diabetes Association. 3. Prevention or delay of type 2 diabetes: standards of medical care in diabetes-2021. Diabetes Care 2021;44(Suppl 1):S34-9.

270. Li R, Bilik D, Brown MB, Zhang P, Ettner SL, Ackermann RT, Crosson JC, Herman WH. Medical costs associated with type 2 diabetes complications and comorbidities. Am J Manag Care 2013;19(5):421-30.

271. Dunlay SM, Shah ND, Shi Q, Morlan B, VanHouten H, Hall Long K, Roger VL. Lifetime costs of medical care after heart failure diagnosis. Circ Cardiovasc Qual Outcomes 2011;4(1):68-75.

272. Paolillo S, Rengo G, Pellegrino T, Formisano R, Pagano G, Gargiulo P, Savarese G, Carotenuto R, Petraglia L, Rapacciuolo A, et al. Insulin resistance is associated with impaired cardiac sympathetic innervation in patients with heart failure. Eur Heart J Cardiovasc Imaging 2015;16(10):1148-53.

273. Centers for Disease Control and Prevention, US Department of Health and Human Services. National diabetes statistics report, 2020. Internet: https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf (accessed 1 October 2021).

274. Curtin LR, Mohadjer LK, Dohrmann SM, Montaquila JM, Kruszan-Moran D, Mirel LB, Carroll M, Hirsch R, Schober S, Johnson C. The National Health and Nutrition Examination Survey: sample design, 1999-2006. Vital Health Stat 2 2012(155):1-39.

275. Curtin LR, Mohadjer LK, Dohrmann SM, Kruszon-Moran D, Mirel LB, Carroll M, Hirsch R, Burt VL, Johnson CL. National Health and Nutrition Examination Survey: sample design, 2007-2010. Vital Health Stat 2 2013(160):1-23.

276. Johnson CL, Dohrmann SM, Burt V, Mohadjer LK. National Health and Nutrition Examination Survey: sample design, 2011–2014. Vital Health Stat 2 2014;162:1-33.

277. National Center for Health Statistics, Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey. Internet: https://www.cdc.gov/nchs/nhanes/index.htm (accessed 1 October 2021).

278. Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, Rand L, Siebert C. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329(14):977-86.

279. Zipf G, Chiappa M, Porter KS, Ostchega Y, Lewis BG, Dostal J. National Health and Nutrition Examination Survey: plan and operations, 1999-2010. Vital Health Stat 1 2013(56):1-37.

280. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and trends in diabetes among adults in the United States, 1988-2012. JAMA 2015;314(10):1021-9.

281. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2019. Diabetes Care 2019;42(Supplement 1):S13-28.

282. Ng E, Vanderloo SE, Geiss L, Johnson JA. Concordance between self-report and a survey-based algorithm for classification of type 1 and type 2 diabetes using the 2011 population-based survey on living with chronic diseases in Canada (SLCDC)-diabetes component. Can J Diabetes 2013;37(4):249-53.

283. Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey: analytic guidelines, 2011-2014 and 2015-2016. Internet: https://wwwn.cdc.gov/nchs/data/nhanes/analyticguidelines/11-16-analytic-guidelines.pdf (accessed 1 October 2021).

284. Centers for Disease Control and Prevention, National Center for Health Statistics. Continuous NHANES web tutorial. Internet: https://wwwn.cdc.gov/nchs/nhanes/tutorials/default.aspx (accessed 1 October 2021).

285. Nichols GA, Hillier TA, Erbey JR, Brown JB. Congestive heart failure in type 2 diabetes: prevalence, incidence, and risk factors. Diabetes Care 2001;24(9):1614-9.

286. Guglin M, Lynch K, Krischer J. Heart failure as a risk factor for diabetes mellitus. Cardiology 2014;129(2):84-92.

287. Preiss D, Zetterstrand S, McMurray JJ, Ostergren J, Michelson EL, Granger CB, Yusuf S, Swedberg K, Pfeffer MA, Gerstein HC, et al. Predictors of development of diabetes in patients with chronic heart failure in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) program. Diabetes Care 2009;32(5):915-20.

288. Kirk JK, Graves DE, Bell RA, Hildebrandt CA, Narayan K. Racial and ethnic disparities in self-monitoring of blood glucose among US adults: a qualitative review. Ethn Dis 2007;17(1):135-42.

289. Lanting LC, Joung IM, Mackenbach JP, Lamberts SW, Bootsma AH. Ethnic differences in mortality, end-stage complications, and quality of care among diabetic patients: a review. Diabetes Care 2005;28(9):2280-8.

290. Ezekowitz JA, Van Walraven C, McAlister FA, Armstrong PW, Kaul P. Impact of specialist follow-up in outpatients with congestive heart failure. CMAJ 2005;172(2):189-94.

291. Flores-Le Roux JA, Comin J, Pedro-Botet J, Benaiges D, Puig-de Dou J, Chillarón JJ, Goday A, Bruguera J, Cano-Perez JF. Seven-year mortality in heart failure patients with undiagnosed diabetes: an observational study. Cardiovasc Diabetol 2011;10(1):39.

292. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2020. Diabetes Care 2020;43(Suppl 1):S14-31.

293. Anand IS, Gupta P. Anemia and iron deficiency in heart failure: current concepts and emerging therapies. Circulation 2018;138(1):80-98.

294. Handelman GJ, Levin NW. Red cell survival: relevance and mechanism involved. J Ren Nutr 2010;20(5):S84-8.

295. Coban E, Ozdogan M, Timuragaoglu A. Effect of iron deficiency anemia on the levels of hemoglobin A1c in nondiabetic patients. Acta Haematol 2004;112(3):126-8.

296. Christy AL, Manjrekar PA, Babu RP, Hegde A, MS R. Influence of iron deficiency anemia on hemoglobin A1c levels in diabetic individuals with controlled plasma glucose levels. Iran Biomed J 2014;18(2):88-93.

297. Altuntaş SÇ, Evran M, Gürkan E, Sert M, Tetiker T. HbA1c level decreases in iron deficiency anemia. Wien Klin Wochenschr 2021;133(3):102-6.

298. Sinha N, Mishra T, Singh T, Gupta N. Effect of iron deficiency anemia on hemoglobin A1c levels. Ann Lab Med 2012;32(1):17-22.

299. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Internet: https://www.who.int/vmnis/indicators/haemoglobin.pdf (accessed 1 October 2021).

300. U.S. Department of Health and Human Services, National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases. MRDR for Adults (Conventional Units). Internet: https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease/laboratory-evaluation/glomerular-filtration-rate-calculators/mdrd-adults-conventional-units (accessed 1 October 2021).

301. Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey, 2015-2016 data documentation, codebook, and frequencies, plasma fasting glucose. Internet: https://wwwn.cdc.gov/Nchs/Nhanes/2015-2016/GLU_I.htm (accessed 1 October 2021).

302. Guo F, Moellering DR, Garvey WT. Use of HbA1c for diagnoses of diabetes and prediabetes: comparison with diagnoses based on fasting and 2-hr glucose values and effects of gender, race, and age. Metab Syndr Relat Disord 2014;12(5):258-68.

303. Fluss R, Faraggi D, Reiser B. Estimation of the Youden index and its associated cutoff point. Biom J 2005;47(4):458-72.

304. Agnelli R. Examples of logistic modeling with the SURVEYLOGISTIC procedure. Interenet: https://support.sas.com/resources/papers/proceedings14/SAS404-2014.pdf (accessed 1 October 2021).

305. Stevens AL, Hansen D, Vandoren V, Westerlaken R, Creemers A, Eijnde BO, Dendale P. Mandatory oral glucose tolerance tests identify more diabetics in stable patients with chronic heart failure: a prospective observational study. Diabetol Metab Syndr 2014;6(1):44.

306. Hoyer A, Rathmann W, Kuss O. Utility of HbA1c and fasting plasma glucose for screening of Type 2 diabetes: a meta-analysis of full ROC curves. Diabet Med 2018;35(3):317-22.

307. Stucchi M, Cantoni S, Piccinelli E, Savonitto S, Morici N. Anemia and acute coronary syndrome: current perspectives. Vasc Health Risk Manag 2018;14:109-18.

308. Montero D, Haider T, Flammer AJ. Erythropoietin response to anaemia in heart failure. Eur J Prev Cardiol 2019;26(1):7-17.

309. Straat M, van Bruggen R, de Korte D, Juffermans NP. Red blood cell clearance in inflammation. Transfus Med Hemother 2012;39(5):353-61.

310. Zhang F, Ye J, Meng Y, Ai W, Su H, Zheng J, Liu F, Zhu X, Wang L, Gao P, et al. Calcium supplementation enhanced adipogenesis and improved glucose homeostasis through activation of Camkii and PI3K/Akt signaling pathway in porcine bone marrow mesenchymal stem cells (pBMSCs) and mice fed high fat diet (HFD). Cell Physiol Biochem 2018;51(1):154-72.

311. Fadda GZ, Thanakitcharu P, Comunale R, Lipson LG, Massry SG. Impaired potassium-induced insulin secretion in chronic renal failure. Kidney Int 1991;40(3):413-7.

312. Kostov K. Effects of magnesium deficiency on mechanisms of insulin resistance in type 2 diabetes: focusing on the processes of insulin secretion and signaling. Int J Mol Sci 2019;20(6):1351.

313. National Institute of Health, National Cancer Institute. Dietary assessment primer: learn more about outliers. Internet: https://dietassessmentprimer.cancer.gov/learn/outliers.html (accessed 1 October 2021).

314. Herrick KA, Rossen LM, Parsons R, Dodd KW. Estimating usual dietary intake from National Health and Nutrition Examination Survey data using the National Cancer Institute method. Vital Health Stat 2 2018;178:1-63.

315. Fung TT, Chiuve SE, McCullough ML, Rexrode KM, Logroscino G, Hu FB. Adherence to a DASH-style diet and risk of coronary heart disease and stroke in women. Arch Intern Med 2008;168(7):713-20.

316. Matthews D, Hosker J, Rudenski A, Naylor B, Treacher D, Turner R. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28(7):412-9.

317. Sumner AE, Cowie CC. Ethnic differences in the ability of triglyceride levels to identify insulin resistance. Atherosclerosis 2008;196(2):696-703.

318. Meigs JB, Porneala B, Leong A, Shiffman D, Devlin JJ, McPhaul MJ. Simultaneous consideration of HbA1c and insulin resistance improves risk assessment in white individuals at increased risk for future type 2 diabetes. Diabetes Care 2020;43(8):e90-2.

319. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr 1997;65(4):1220S-8S.

320. Allison PD. Logistic regression using SAS: theory and application. 2nd ed. Cary: SAS institute, 2012.

321. Phillips CM, Harrington JM, Perry IJ. Relationship between dietary quality, determined by DASH score, and cardiometabolic health biomarkers: a cross-sectional analysis in adults. Clin Nutr 2019;38(4):1620-8.

322. Jacobs S, Boushey CJ, Franke AA, Shvetsov YB, Monroe KR, Haiman CA, Kolonel LN, Le Marchand L, Maskarinec G. A priori-defined diet quality indices, biomarkers and risk for type 2 diabetes in five ethnic groups: the Multiethnic Cohort. Br J Nutr 2017;118(4):312-20.

323. Esfandiari S, Bahadoran Z, Mirmiran P, Tohidi M, Azizi F. Adherence to the dietary approaches to stop hypertension trial (DASH) diet is inversely associated with incidence of insulin resistance in adults: the Tehran lipid and glucose study. J Clin Biochem Nutr 2017;61(2):123-9.

324. Englyst HN, Cummings JH. Digestion of the polysaccharides of some cereal foods in the human small intestine. Am J Clin Nutr 1985;42(5):778-87.

325. MacNeil S, Rebry RM, Tetlow IJ, Emes MJ, McKeown B, Graham TE. Resistant starch intake at breakfast affects postprandial responses in type 2 diabetics and enhances the glucose-dependent insulinotropic polypeptide–insulin relationship following a second meal. Appl Physiol Nutr Metab 2013;38(12):1187-95.

326. Snook LA, Nelson EM, Dyck DJ, Wright DC, Holloway GP. Glucose-dependent insulinotropic polypeptide directly induces glucose transport in rat skeletal muscle. Am J Physiol Regul Integr Comp Physiol 2015;309(3):R295-303.

327. Adeva-Andany MM, González-Lucán M, Fernández-Fernández C, Carneiro-Freire N, Seco-Filgueira M, Pedre-Piñeiro AM. Effect of diet composition on insulin sensitivity in humans. Clin Nutr ESPEN 2019;33:29-38.

328. Sánchez M, de la Sierra A, Coca A, Poch E, Giner V, Urbano-Márquez A. Oral calcium supplementation reduces intraplatelet free calcium concentration and insulin resistance in essential hypertensive patients. Hypertension 1997;29(1 Pt 2):531-6.

329. Chatterjee R, Slentz C, Davenport CA, Johnson J, Lin PH, Muehlbauer M, D'Alessio D, Svetkey LP, Edelman D. Effects of potassium supplements on glucose metabolism in African Americans with prediabetes: a pilot trial. Am J Clin Nutr 2017;106(6):1431-8.

330. Mooren FC, Krüger K, Völker K, Golf SW, Wadepuhl M, Kraus A. Oral magnesium supplementation reduces insulin resistance in non-diabetic subjects - a double-blind, placebo-controlled, randomized trial. Diabetes Obes Metab 2011;13(3):281-4.

331. Edwards KM, Wilson KL, Sadja J, Ziegler MG, Mills PJ. Effects on blood pressure and autonomic nervous system function of a 12-week exercise or exercise plus DASH-diet intervention in individuals with elevated blood pressure. Acta Physiol (Oxf) 2011;203(3):343-50.

332. Flaa A, Aksnes TA, Kjeldsen SE, Eide I, Rostrup M. Increased sympathetic reactivity may predict insulin resistance: an 18-year follow-up study. Metabolism 2008;57(10):1422-7.

333. Straznicky NE, Grima MT, Sari CI, Lambert EA, Phillips SE, Eikelis N, Kobayashi D, Hering D, Mariani JA, Dixon JB. Reduction in peripheral vascular resistance predicts improvement in insulin clearance following weight loss. Cardiovasc Diabetol 2015;14(1):113.

334. Stocker SD, Madden CJ, Sved AF. Excess dietary salt intake alters the excitability of central sympathetic networks. Physiol Behav 2010;100(5):519-24.

335. Joseph P, Dokainish H, McCready T, Budaj A, Roy A, Ertl G, Gomez-Mesa JE, Leong D, Ezekowitz J, Hage C, et al. A multinational registry to study the characteristics and outcomes of heart failure patients: The global congestive heart failure (G-CHF) registry. Am Heart J 2020;227:56-63.

336. DeVore AD, Thomas L, Albert NM, Butler J, Hernandez AF, Patterson JH, Spertus JA, Williams FB, Turner SJ, Chan WW, et al. Change the management of patients with heart failure: Rationale and design of the CHAMP-HF registry. Am Heart J 2017;189:177-83.

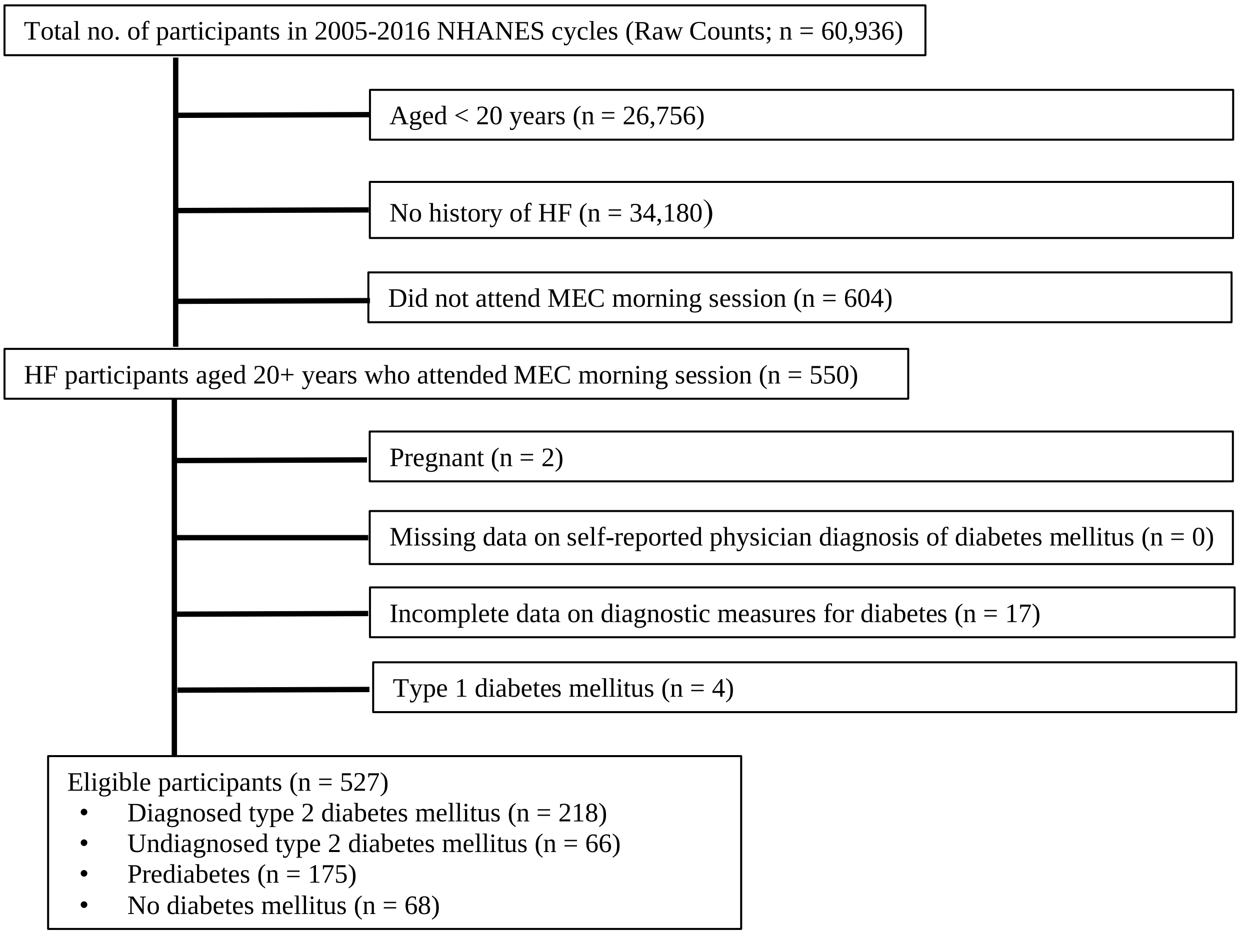
337. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, Ferrari R, Piepoli MF, Delgado Jimenez JF, Metra M, et al. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. Eur J Heart Fail 2016;18(6):613-25.

338. Lam CS, Anand I, Zhang S, Shimizu W, Narasimhan C, Park SW, Yu CM, Ngarmukos T, Omar R, Reyes EB, et al. Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry. Eur J Heart Fail 2013;15(8):928-36.

339. Center for Disease Control and Prevention Diabetes Cost-effectiveness Group. Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. JAMA 2002;287(19):2542-51.

APPENDIX A

SUPPLEMENTAL MATERIALS FOR CHAPTER 3



Appendix A.1. Analytic Sample Selection. Abbreviations: HF, heart failure; NHANES, National Health and Nutrition Examination Survey; MEC, mobile examination center.

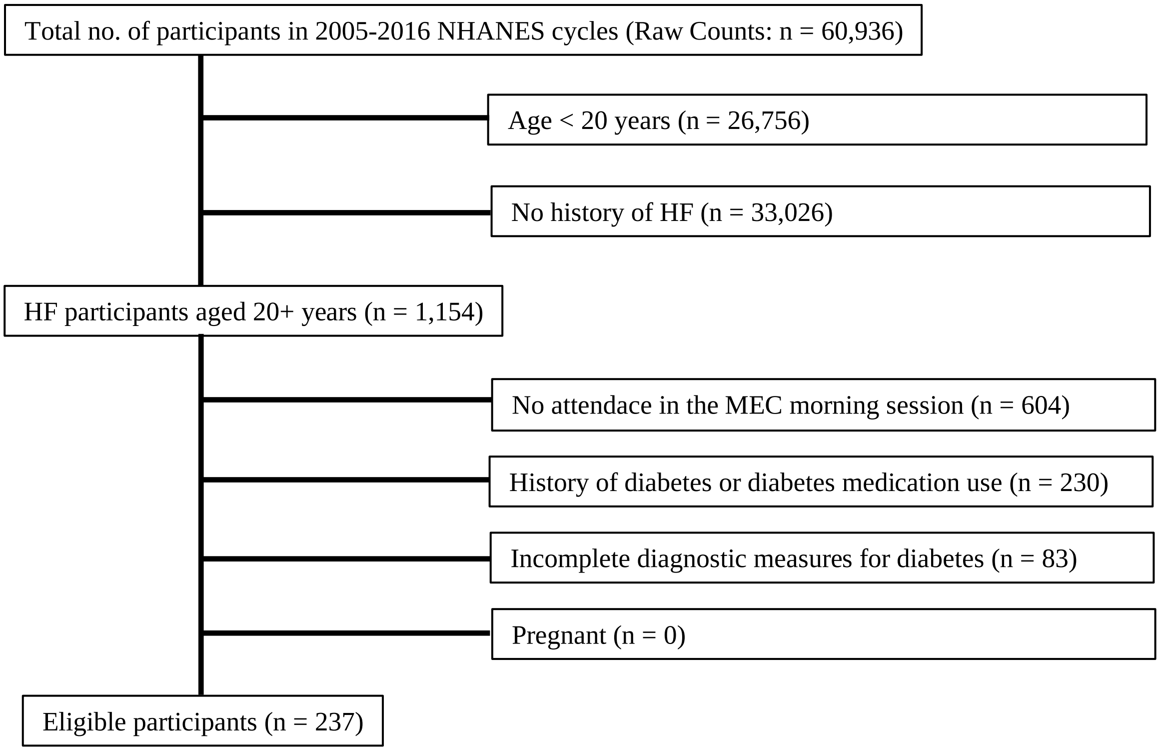
Appendix A.2. Sociodemographic and Health Characteristics of Participants with Heart Failure Aged 20+ Years by Attendance of Mobile Examination Center Session

	Attended MEC Morning Session (n=550)	Did Not Attend MEC Morning Session (n=604)	P Value[a]
Sociodemographic Characteristics			
Age, mean (SE)	65.9 (0.7)	67.0 (0.7)	0.235
Gender, No. (%)			
Male	287 (50.7)	344 (50.8)	0.997
Female	263 (49.3)	260 (49.2)	
Race/Ethnicity, No. (%)			
Non-Hispanic White	288 (71.6)	300 (68.4)	0.571
Non-Hispanic Black	136 (14.4)	173 (17.5)	
All Hispanic	97 (8.1)	97 (8.0)	
Other	29 (5.9)	34 (6.1)	
Education, No. (%)[b]			
Less than High School	219 (32.8)	208 (27.8)	0.363
High School Graduate	131 (25.7)	161 (27.4)	
More than High School	199 (41.4)	234 (44.9)	
Poverty Income Ratio, No. (%)[b]			
≤ 1.30	211 (35.0)	232 (31.8)	0.347
1.31-3.50	200 (43.3)	228 (49.7)	
≥ 3.51	78 (21.8)	88 (18.5)	
Medical History, No. (%)			
Angina	115 (22.4)	147 (26.3)	0.209
Coronary Heart Disease	198 (35.6)	251 (42.6)	0.053
Hypertension	443 (76.8)	484 (79.0)	0.486
Myocardial Infarction	235 (42.6)	253 (42.9)	0.946
Stroke	119 (22.3)	122 (19.3)	0.290
Duration of Heart Failure (Years)[b]			
0-5	237 (44.2)	286 (48.2)	0.251
6+	300 (55.8)	305 (51.8)	
Hospitalization in the Past 12 Months[b]			
None	323 (61.4)	339 (57.8)	0.324
1+	226 (38.6)	262 (42.2)	
Medication Use, No. (%)			
Angiotensin-converting Enzyme Inhibitors	203 (37.4)	183 (31.7)	0.106
Angiotensin II Receptor Blockers	85 (13.9)	96 (18.7)	0.111
Beta-blockers	331 (59.9)	352 (61.8)	0.609
Loop Diuretics	238 (42.7)	257 (44.1)	0.666
Nitrates and Vasodilators	106 (18.8)	118 (17.8)	0.715

[a] P-value indicates significance of differences between the groups using survey-weighted general linear models for continuous variables and the Rao-Scott F adjusted chi-square tests for categorical variables.; [b] Raw counts did not sum to group total due to missing values.; Abbreviations: MEC, mobile examination center; No, numbers; SE, standard error.

APPENDIX B

SUPPLEMENTAL MATERIALS FOR CHAPTER 4



Appendix B.1. Flow Chart of Analytic Sample Selection. HF = heart failure; NHANES = National Health and Nutrition Examination Survey; MEC = mobile examination center.

Appendix B.2. Sociodemographic and Medical Characteristics of Included and Excluded Participants with Heart Failure

Characteristics	Included Participants (n = 237)	Excluded Participants (n = 917)	P Value[*]
Age, mean (SE)	65.1 (1.1)	66.9 (0.5)	0.100
Female, %	42.2	51.5	0.051
Race/Ethnicity, %			
Non-Hispanic White	77.1	67.7	0.007
Non-Hispanic Black	10.5	17.7	
All Hispanic	6.4	8.6	
Other	6.0	6.0	
Education, %			
Less than High School	29.8	30.5	0.461
High School Graduate	23.1	27.7	
More than High School	47.1	41.9	
Poverty Income Ratio, %			
≤1.30	32.0	33.9	0.862
1.31-3.50	46.3	46.5	
>3.50	21.7	19.6	
Angina, %	24.6	24.2	0.914
Coronary Heart Disease, %	33.0	41.1	0.038
Myocardial Infarction, %	46.2	41.6	0.321
Hypertension, %	68.7	80.9	0.001
Stroke, %	18.1	21.7	0.308

* P-value indicates significance of differences between the groups using survey-weighted general linear models for continuous variables and the Rao-Scott F adjusted chi-square tests for categorical variables. Abbreviation: No, numbers; SE, standard error.

APPENDIX C

SUPPLEMENTAL MATERIALS FOR CHAPTER 5

Appendix C.1. Criteria for Determining Dietary Approaches to Stop Hypertension Diet Index Scores

DASH Diet Index Components/Score	**1 Point**	**2 Points**	**3 Points**	**4 Points**	**5 Points**
Fruits, cup eq.	≤ 0.4800	0.4800-0.7210	0.7210-0.9440	0.9440-1.2950	> 1.2950
Vegetables, cup eq.	≤ 0.6213	0.6213-0.8368	0.8368-1.0250	1.0250-1.2500	> 1.2500
Nuts and Legumes, cup eq.	≤ 0.4050	0.4050-0.5300	0.5300-0.7392	0.7392-1.1430	> 1.1430
Whole Grains, oz eq.	≤ 0.3190	0.3190-0.6090	0.6090-0.8260	0.8260-1.0550	> 1.0550
Low-fat Dairy, cup eq.	≤ 0.0084	0.0084-0.0205	0.0205-0.0362	0.0362-0.1920	> 0.1920
Sodium, mg[1]	> 3,560.0	3,030.0-3,560.0	2,580.0-3,030.0	2,200.0-2,580.0	≤ 2,200.0
Red and Processed Meats, oz eq.[1]	> 3.2950	2.9550-3.2950	2.1630-2.9550	1.7300-2.1630	≤ 1.7300
Sweetened Beverages, tsp eq.[1]	> 7.9900	3.7140-7.9900	2.0000-3.7140	0.5800-2.0000	≤ 0.5800

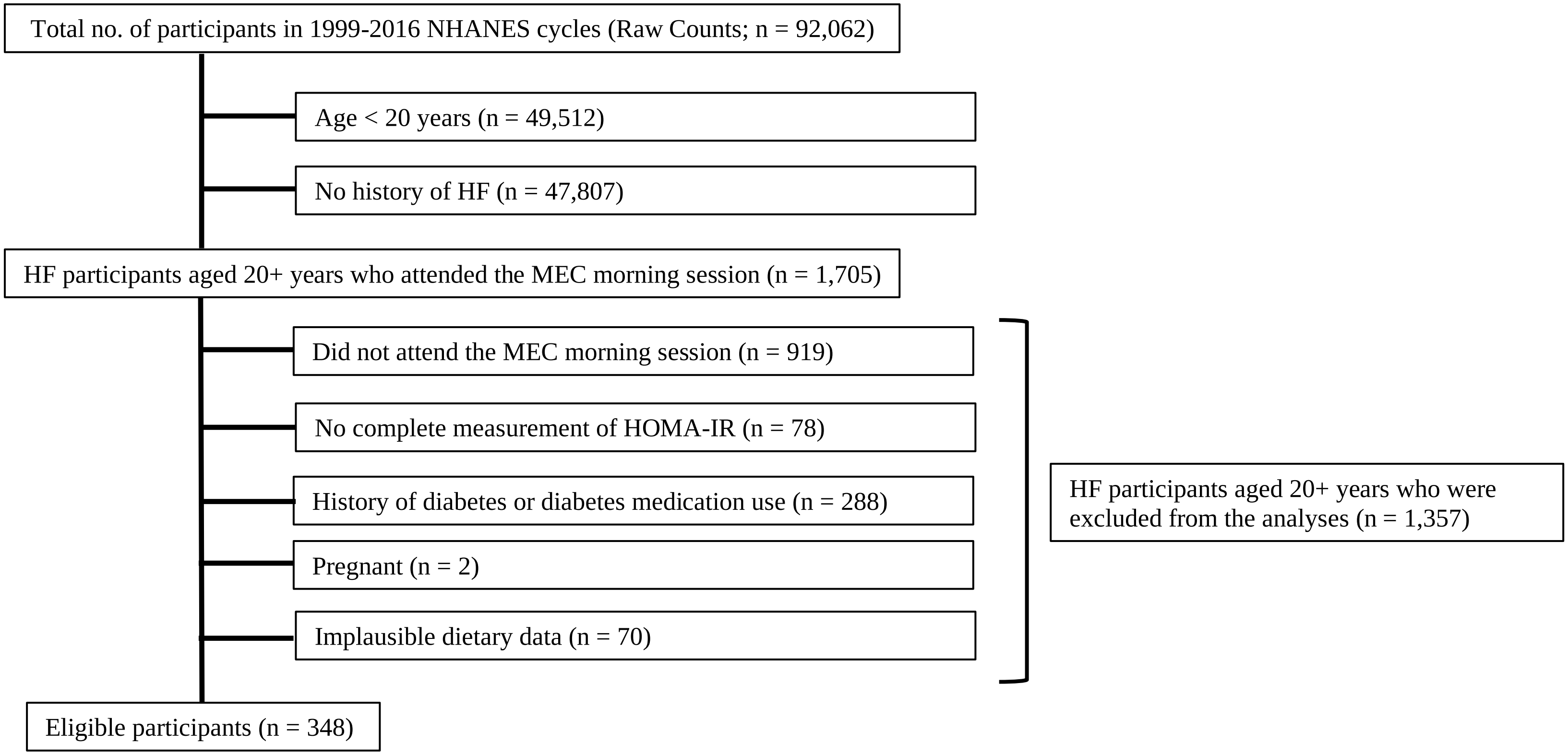
[1] Scores were calculated based on a reverse scoring method. Abbreviations: cup eq., cup equivalent; DASH, dietary approaches to stop hypertension; oz eq., ounce equivalent; tsp eq., teaspoon equivalent.

Appendix C.2. Associations of Sample Characteristics with the Highest Level of Insulin Resistance among Heart Failure Patients in Simple Logistic Regression Models

Characteristics	**OR (95% CI)**	**P-Value**
Sociodemographic Characteristics		
Age ≥ 65 Years (Ref. < 65 Years)	0.718 (0.400-1.287)	0.264
Male (Ref. Female)	0.850 (0.488-1.481)	0.564
Racial/Ethnic Minorities (Ref. Non-Hispanic White)	1.681 (0.909-3.110)	0.097
Not Married or Living with Partner (Ref. Married or Living with Partner)	1.176 (0.685-2.018)	0.555
Education (Ref. Less than High School)		
High School Graduate	0.957 (0.409-2.243)	0.920
More than High School	0.989 (0.482-2.028)	0.976
Without Job (Ref. With Job)	0.522 (0.269-1.015)	0.052
Poverty Income Ratio (Ref. ≤ 1.30)		
1.31-3.50	1.057 (0.552-2.023)	0.866
> 3.50	0.908 (0.388-2.126)	0.823
Food Insecurity (Ref. Food Security)	0.842 (0.379-1.871)	0.670
Physical Examination, Laboratory Values, and Behavioral Factors		
BMI Categories (Ref. Normal Weight, < 25 kg/m^2)		
Overweight (25-29 kg/m^2)	6.774 (2.089-21.965)	0.002
Obese (≥ 30 kg/m^2)	20.466 (6.584-63.616)	< 0.001
Abnormal Abdominal Fat (Ref. Normal Abdominal Fat)	6.672 (3.485-12.773)	< 0.001
Systolic Blood Pressure (Ref. < 120 mm Hg)		
120-139 mm Hg	1.148 (0.602-2.189)	0.673
≥ 140 mm Hg	0.590 (0.304-1.146)	0.118
Diastolic Blood Pressure ≥ 80 mm Hg (Ref. < 80 mm Hg)	0.928 (0.433-1.992)	0.848
High Total Cholesterol Levels (Ref. Normal Levels)	0.610 (0.319-1.164)	0.133
High Serum Triglyceride Levels (Ref. Normal Levels)	3.264 (1.669-6.384)	0.001
Low HDL-Cholesterol Levels (Ref. Normal Levels)	2.686 (1.391-5.188)	0.004
High LDL-Cholesterol Levels (Ref. Normal Levels)	0.932 (0.505-1.719)	0.819
Dietary Energy (Ref. Tertile 1; < 1560 kcal)		
Tertile 2 (1560-1949 kcal)	0.930 (0.469-1.847)	0.836
Tertile 3 (≥ 1950 kcal)	1.516 (0.821-2.801)	0.182
Alcohol Drinker (Ref. Not Drinking)	0.797 (0.420-1.511)	0.484
Current Smoker (Ref. Not Smoking)	0.418 (0.195-0.898)	0.026
No Physical Activity (Ref. Physical Activity)	1.166 (0.576-2.361)	0.667
Medical History		
Family History of Diabetes (Ref. No)	1.344 (0.758-2.381)	0.381
≥ CKD Stage 3a (Ref. CKD < Stage 3a)	0.576 (0.296-1.121)	0.104
History of Angina (Ref. No History)	0.865 (0.460-1.624)	0.649
History of Coronary Heart Disease (Ref. No History)	0.696 (0.391-1.239)	0.216
History of Myocardial Infarction (Ref. No History)	1.246 (0.684-2.272)	0.469
History of Hypertension (Ref. No History)	0.948 (0.507-1.772)	0.865
History of Stroke (Ref. No History)	0.440 (0.207-0.934)	0.033
No Health Insurance (Ref. Health Insurance)	1.280 (0.388-4.217)	0.683
4+ Outpatient Care Over Past 12 months (Ref. 0-3)	0.733 (0.360-1.492)	0.389
Inpatient Care Over Past 12 months (Ref. None)	0.621 (0.309-1.247)	0.178
6+ Years of Duration of Heart Failure (Ref. 0-5 Years)	1.308 (0.751-2.275)	0.340
Medication Use		
ACEi and/or ARBs (Ref. No Use)	1.417 (0.773-2.598)	0.258
β-blockers (Ref. No Use)	1.370 (0.764-2.457)	0.288
Loop Diuretics (Ref. No Use)	1.742 (0.900-3.370)	0.099
Nitrates and Vasodilators (Ref. No Use)	0.986 (0.469-2.072)	0.970
Statin (Ref. No Use)	1.305 (0.700-2.431)	0.399

Anticoagulation (Ref. No Use)	0.709 (0.322-1.559)	0.390

Abnormal abdominal fat was defined as waist circumference ≥ 102 cm for male or ≥ 88 cm for female. High total cholesterol levels were defined as total cholesterol levels ≥ 200 mg/dL. High serum tri-glyceride levels were defined as serum triglyceride levels ≥ 150 mg/dL. Low HDL-cholesterol levels were defined as HDL-cholesterol levels < 40 mg/dL for male or < 50 mg/dL for female. High LDL-cholesterol levels were defined as LDL-cholesterol levels ≥100 mg/dL. Abbreviations: ACEi, angio-tensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BMI, body mass index; CKD, chronic kidney disease; OR, odds ratio; Ref. reference group.



Appendix C.3. Flow Chart of Analytic Sample Selection - HF, heart failure; HOMA-IR, homeostatic model assessment-insulin resistance; MEC, mobile examination center; NHANES, National Health and Nutrition Examination Survey.

Appendix C.4. Sociodemographic and Health Characteristics of Included and Excluded Participants with Heart Failure

Characteristics	**Included Participants (n = 348)**	**Excluded Participants (n = 1,357)**	**P Value[1]**
Age, Mean (SE)	65.5 (0.8)	66.7 (0.5)	0.177
Gender, %			
Male	57.2	48.6	0.024
Female	42.8	51.4	
Race/Ethnicity, %			
Non-Hispanic White	80.6	69.4	0.001
Non-Hispanic Black	8.9	16.5	
All Hispanic	6.2	8.9	
Other	4.3	5.3	
Education, %			
Less than High School	33.1	35.1	0.630
High School Graduate	28.5	25.1	
More than High School	38.4	39.9	
Angina, %	27.2	27.3	0.984
Coronary Heart Disease, %	38.0	41.6	0.317
Heart Attack, %	44.3	43.8	0.900
Hypertension, %	66.1	76.6	0.005
Stroke, %	20.5	19.7	0.815

[1] P-value indicates significance of differences between the groups using survey-weighted general linear models for continuous variables and the Rao-Scott F adjusted chi-square tests for categorical variables. Abbreviation: SE, standard error.

Appendix C.5. Intakes of Nutrient and Food Group across Dietary Approaches to Stop Hypertension Diet Adherence Index Quartiles

		DASH Diet Adherence Index			
	ALL	**Quartile 1**	**Quartile 2**	**Quartile 3**	**Quartile 4**
Total Energy, Median (IQR), kcal	1,788 (1,449-2,186)	1,921 (1,582-2,327)	1,930 (1,575-2,321)	1,662 (1,336-2,041)	1,654 (1,339-2,026)
Macronutrient Consumption, Median (IQR)					
Protein, g	68.4 (55.2-83.6)	71.4 (58.2-86.0)	70.4 (57.2-85.0)	65.0 (51.8-80.1)	66.9 (54.0-85.0)
Total Fat, g	66.2 (50.9-84.4)	73.7 (57.9-92.7)	74.0 (58.1-92.4)	64.3 (49.8-81.3)	55.3 (43.0-69.8)
Saturated Fatty Acids, g	21.5 (16.8-27.0)	24.2 (19.4-30.2)	24.1 (19.3-29.7)	20.4 (16.1-25.2)	18.1 (14.4-22.5)
Monounsaturated Fatty Acids, g	23.9 (18.1-30.8)	26.6 (20.7-33.5)	27.1 (21.1-34.0)	23.7 (18.2-30.2)	19.1 (14.7-24.5)
Polyunsaturated Fatty Acids, g	14.6 (10.7-19.5)	15.8 (11.7-20.9)	15.7 (11.5-20.6)	14.3 (10.5-19.4)	13.0 (9.7-17.2)
Cholesterol, mg	242.1 (182.6-317.7)	296.8 (232.2-374.2)	286.6 (223.7-362.3)	208.4 (160.0-266.9)	197.5 (152.1-253.8)
Carbohydrates, g	223.2 (182.5-271.5)	230.2 (190.6-276.6)	239 (197.4-284.8)	204.9 (165.8-251.4)	216.5 (177.5-263.5)
Dietary Fiber, g	14.0 (10.9-17.6)	10.1 (7.9-12.5)	13.9 (11.4-16.6)	13.0 (10.3-16.2)	18.1 (14.9-21.9)
Macronutrient Consumption Ratio, Median (IQR)					
Protein, % of Total Energy Intake	15.3 (13.7-17.0)	14.7 (13.3-16.2)	14.6 (13.2-16.2)	15.6 (14.1-17.2)	16.2 (14.7-18.1)
Total Fat, % of Total Energy Intake	33.2 (29.9-36.6)	33.9 (30.9-37.3)	34.4 (31.5-37.6)	34.5 (31.6-37.8)	30.0 (27.4-32.8)
Carbohydrates, % of Total Energy Intake	50.0 (46.4-53.9)	47.8 (44.3-51.8)	49.5 (46.1-53.3)	49.1 (45.8-52.4)	52.9 (49.4-56.7)
Micronutrient Consumption, Median (IQR)					
Vitamin E, mg α-Tocopherol eq.	6.3 (4.7-8.2)	5.3 (4.1-7.0)	6.3 (4.8-8.2)	6.3 (4.8-8.3)	7.0 (5.4-9.1)
Vitamin A, µg RAE	598.6 (409.9-855.4)	443.3 (313.2-615.4)	528.3 (367.3-735.7)	601.9 (428.1-835.7)	840.2 (606.3-1,129.5)
Thiamin, mg	1.44 (1.15-1.79)	1.43 (1.15-2.75)	1.48 (1.18-1.83)	1.39 (1.10-1.74)	1.45 (1.17-1.84)
Riboflavin, mg	1.96 (1.53-2.47)	1.87 (1.46-2.37)	1.98 (1.54-2.49)	1.92 (1.50-2.42)	2.02 (1.61-2.55)
Niacin, mg	20.9	22.0	21.8	19.6	20.5

	(16.6-26.3)	(17.8-26.8)	(17.2-26.9)	(15.3-24.6)	(16.4-26.4)
Vitamin B6, mg	1.72 (1.34-2.20)	1.57 (1.22-1.97)	1.76 (1.37-2.21)	1.6 (1.24-2.05)	1.92 (1.50-2.45)
Total Folate, µg	350.4 (287.4-425.3)	333.7 (277.3-395.8)	346.9 (284.2-413.9)	341.9 (275.0-414.2)	377.0 (309.7-476.5)
Vitamin B12, µg	4.4 (3.2-5.9)	4.5 (3.3-6.0)	4.5 (3.3-6.0)	4.4 (3.2-5.9)	4.2 (3.2-5.7)
Vitamin C, mg	75.0 (49.4-110.0)	47.0 (31.4-67.4)	74.1 (52.0-102.7)	67.2 (45.4-95.7)	112.8 (80.1-153.8)
Calcium, mg	788.5 (617.2-985.9)	722.0 (567.4-910.1)	744.1 (582.2-929.6)	809.2 (640.3-1,008.2)	868.5 (691.4-1,077.1)
Phosphorus, mg	1,166 (934-1,437)	1,136 (915-1,399)	1,176 (944-1,438)	1,123 (891-1,396)	1,211 (973-1,511)
Magnesium, mg	249.2 (199.9-307.0)	203.6 (164.7-247.9)	246.9 (202.2-296.2)	242.7 (194.5-298.3)	294.0 (240.2-359.7)
Iron, mg	13.6 (10.8-17.1)	13.1 (10.4-16.3)	14.1 (11.1-17.5)	12.9 (10.2-16.2)	14.2 (11.3-18.1)
Zinc, mg	10.3 (8.1-13.0)	10.4 (8.3-13.0)	11.2 (8.9-14.0)	9.6 (7.6-12.2)	9.9 (7.8-12.6)
Copper, mg	1.2 (0.9-1.4)	0.9 (0.8-1.1)	1.2 (1.0-1.5)	1.0 (0.8-1.2)	1.4 (1.1-1.7)
Sodium, mg	2,939 (2,328-3,662)	3,293 (2,662-4,031)	3,164 (2,534-3,874)	2,720 (2,143-3,379)	2,664 (2,120-3,350)
Potassium, mg	2,443 (1,938-3,026)	2,047 (1,632-2,515)	2,425 (1,946-2,954)	2,365 (1,869-2,919)	2,829 (2,297-3,472)
Selenium, µg	91.7 (74.8-111.5)	101.3 (83.2-121.0)	93.8 (76.9-112.9)	87.6 (71.3-106.6)	86.9 (70.7-106.3)
Food Group Consumption, Median (IQR)					
Total Fruits, cup eq.	0.8 (0.5-1.3)	0.4 (0.3-0.7)	0.7 (0.4-1.1)	0.9 (0.5-1.3)	1.2 (0.8-1.8)
Total Vegetables, cup eq.	1.4 (1.0-1.8)	1.1 (0.8-1.5)	1.4 (1.1-1.8)	1.2 (0.8-1.5)	1.8 (1.4-2.3)
Vegetables Except Potatoes and Legumes, cup eq.	0.9 (0.6-1.4)	0.7 (0.4-1.0)	1.0 (0.7-1.3)	0.8 (0.5-1.2)	1.3 (0.9-1.9)
Nuts and Legumes, cup eq.	0.6 (0.3-1.1)	0.3 (0.2-0.6)	0.7 (0.4-1.1)	0.7 (0.4-1.2)	0.7 (0.4-1.2)
Total Grains, oz. eq.	5.7 (4.8-6.9)	5.8 (4.9-6.9)	6.1 (5.2-7.3)	5.6 (4.6-6.6)	5.3 (4.5-6.5)
Whole Grains, oz. eq.	0.7	0.5	0.6	0.7	1.0

	(0.4-1.0)	(0.3-0.8)	(0.4-0.9)	(0.4-1.0)	(0.5-1.4)
Total Protein Foods, oz. eq.	4.7 (3.5-6.2)	5.6 (4.2-7.1)	4.9 (3.7-6.4)	4.6 (3.3-6.0)	4.2 (3.1-5.6)
Red and Processed Meats, oz. eq.	2.4 (1.8-3.1)	3.0 (2.1-3.7)	2.6 (1.9-3.3)	2.3 (1.7-2.9)	2.2 (1.7-2.8)
Total Dairy, cup eq.	1.3 (1.0-1.7)	1.2 (0.8-1.6)	1.3 (1.0-1.7)	1.3 (1.0-1.7)	1.4 (1.1-1.9)
Low-fat Dairy, cup eq.	0.1 (0.0-0.3)	0.1 (0.0-0.3)	0.0 (0.0-0.2)	0.1 (0.0-0.3)	0.1 (0.0-0.3)
Discretionary Oil, g	15.8 (10.1-23.4)	17.8 (11.5-26.3)	14.6 (9.1-22.1)	17.5 (11.3-25.7)	14.8 (9.5-21.5)
Discretionary Solid Fat, g	33.7 (25.1-44.3)	38.5 (29.5-49.3)	40.1 (30.9-50.6)	30.6 (23.1-39.3)	27.4 (20.8-35.3)
Added Sugar, tsp. eq.	14.3 (9.1-20.9)	20.2 (14.5-27.3)	16.8 (11.6-23.3)	11.8 (7.8-17.7)	10.5 (6.8-15.5)
Sweetened Beverages, tsp. eq.	2.6 (0.8-5.9)	5.1 (1.4-10.7)	3.2 (0.9-6.8)	2.4 (0.7-5.2)	1.6 (0.5-3.6)

Intakes of nutrient and food were adjusted for age, gender, race/ethnicity, body mass index, 24-hour dietary recalls (first recall administered during the MEC session or second recall administered by phone 3-10 days later), and the day-of-week of 24-hour recall (Monday-Thursday or Friday-Sunday). Abbreviations: DASH, dietary approaches to stop hypertension; eq, equivalent; IQR, interquartile range; oz, ounce; RAE, retinol activity equivalent; tsp, teaspoon.

Appendix C.6. Total Numbers and Rates of Missing Values for Included Variables in Logistic Regression Model 3

Variables (n = 348)	**Total Number of Missing Values**	**Rate of Missing Values (%)**
Age	0	0
Gender	0	0
Race/Ethnicity	0	0
Dietary Energy	0	0
Current Smoker	0	0
Body Mass Index	14	4.0
Abnormal Abdominal Fat	24	6.9
Serum Triglyceride	4	1.1
HDL-Cholesterol	0	0
History of Stroke	0	0

Abbreviation: HDL, high-density lipoprotein.