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Erica N. Davis

Relationships among Dietary Patterns, Metabolites, and Symptoms in Persons with Heart Failure

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An Abstract of
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Abstract

Relationships among Dietary Patterns, Metabolites, and Symptoms in Persons with Heart Failure

By: Erica Davis

Black Americans have a disproportionate rate of onset with heart failure (HF) at an earlier age and a 30-44% higher 5-year mortality rate compared to other racial and ethnic groups. Symptom burden is a significant health concern among Black populations with HF and may be addressed by examining the relationships between diet and inflammatory processes to identify symptom triggers and subsequently guide intervention by diet modification. The dietary gut derived metabolite trimethylamine-N-oxide (TMAO) has been noted as a key contributor to HF severity and has interconnections with inflammatory processes in the heart and blood vessels as well as dietary links. The purpose of this study was to examine associations of an inflammatory diet, the specific gut derived metabolite (TMAO), an inflammatory biomarker tumor necrosis factor-alpha (TNF-α), and symptoms in the Black HF population.

For this cross-sectional study, 30 Black men and women with HF, who were between the ages of 30-80 years, were enrolled from the Emory outpatient cardiology clinics. Measures included sociodemographic and clinical data, questionnaires (heart failure symptom survey, multidimensional social support, and the Center for Epidemiology Studies scale for depressive symptoms), a food frequency questionnaire with a calculated dietary inflammatory index score (DII), and biomarkers of TMAO and TNF-α. Analysis included correlations and linear regression. Covariates included age, sex, left ventricular ejection fraction, social support, comorbidities (Charlson comorbidity index) and lifestyle factors of smoking, alcohol intake, body mass index (BMI), and physical activity.

Findings from this study included a moderate correlation between TNF-α and TMAO ($r=.28$, $p=.138$). No significant relationships with DII and TMAO nor DII and TNF-α were detected. Although models with TNF-α and TMAO accounted for 37%-45.9% of variance in physical HF symptoms, only the covariates were significant predictors.

These data suggest that, in addition to managing physical inflammatory influences on HF symptoms, other factors to consider include a person's age, metabolite levels, comorbidities, lifestyle, ejection fraction and needs related to life quality. This information may help clinicians as it can assist with understanding the individual and subjective nature of HF physical and psychological symptoms along with the influencing factors of the person experiencing them.

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Chapter 1

Introduction

Statement of the Problem

Approximately 6.2 million Americans were diagnosed with heart failure (HF) between 2013 and 2016, and over 800,000 are diagnosed annually.[1,2] Acute HF episodes in the United States account for over one million hospital stays per year.[2] In addition to this high societal burden, persons with HF experience progressive decline in functional status and distressing physical symptoms leading to reduced quality of life (QOL).[3] Black Americans have higher rates of hypertension and cardiometabolic risk for HF compared to the overall population, develop earlier onset of HF, and have a 30-44% higher 5-year mortality rate compared to other races.[3]

HF is characterized by high overall symptom burden including fatigue, dyspnea, orthopnea, and edema. In addition, up to 21.5% of HF patients experience significant depressive symptoms, much higher than 7.1% in adults without HF.[4] While symptoms in HF are attributed to oxidative stress, congestion, and fluid overload, increased inflammation also plays a role.[5] Contributors to inflammation in HF involve pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), which may result in cardiac dysfunction, increased mortality,[6] and depressive symptoms.[7] Gut-derived metabolites also contribute to inflammation and may be linked to a pro-inflammatory diet,[8] a diet that consists of foods high in fat and carbohydrates which may contribute to increased HF symptoms and severity.[9] Poor dietary patterns in the Black population may contribute to an increased vulnerability for these relationships.[10] Although symptoms may be reflective of HF severity, they may also be related to worsening HF or pathological changes that are not reflected in a clinical visit. Therefore, health professionals may not get a full glimpse of the symptom triggers through traditional measures in HF such as brain natriuretic peptide; studies involving another potential biomarker, like trimethylamine-N-oxide TMAO, may yield a fuller clinical picture of the patient's disease process.[11] Studies of symptom severity in Black adults with HF are limited, and the few studies available report functional impairment, depressive symptoms, and low social support from caregivers yielding worse outcomes than other ethnic groups.[12] Greater understanding of the

physiological and behavioral contributors, such as diet, to both physical and depressive symptoms is essential to develop more precise interventions for Black adults with HF.

Recent studies report significant links between dietary metabolism, the gut microbiota, and acute HF.[13,14] Trimethylamine-N-oxide (TMAO), a gut microbial metabolite of choline and L-carnitine, is associated with cardiovascular ischemia, inflammation, chronic kidney disease, hypertension, and poor survival.[15-18] TMAO is derived from foods that may comprise a pro-inflammatory diet. The inflammatory diet includes the following food categories: dairy products, especially those high in fat, red meat, sugar sweetened drinks, fried foods, margarine, and certain fish.[19] Guidelines in HF care call for relief of symptom burden, and studies suggest dietary modification may improve cardiac function and alleviate disease severity.[20,21] Diets in Southern Black culture typically reflect large amounts of pro-inflammatory foods from red meat, fried poultry, and other foods, and fast foods containing high amounts of cholesterol and fat.[10,22] The interconnections of the inflammatory diet, the metabolites, and symptoms may illuminate a metabolic pathway for how diet contributes to symptom burden in the Black HF population. Greater knowledge of the relationships among the inflammatory process, dietary patterns, the gut metabolite TMAO, and physical and psychological symptoms in HF is needed to inform dietary modifications, which in HF care, have traditionally focused on reducing dietary sodium and fluid intake.[21,23]

Purpose

The **purpose** of this study was to explore dietary influences on inflammation as a pathway for symptoms in Black HF patients (n=31) and to examine relationships among physical and psychological symptoms, pro-inflammatory dietary patterns (dietary inflammation index, DII), inflammation (TNF-α), and the metabolite TMAO while controlling for covariates of age, comorbidities, sex, lifestyle factors (LIS [alcohol, smoking, obesity, physical activity]), social support (Multidimensional Scale of Perceived Social Support, MPSSS), and left ventricular ejection fraction (LVEF). The heart failure symptom survey (HFSS) and the Center for Epidemiological Studies Depression Scale (CES-D) were used respectively to assess physical and depressive symptoms associated with heart failure.

Specific Aims and Hypotheses

Specific Aim 1: Investigate the relationships among pro-inflammatory diet (DII), inflammation (TNF-α), and the gut metabolite TMAO. **H1a.** Increased DII is related to increased TNF-α. **H1b.** Increased DII is related to increased TMAO. **H1c.** The greater the TMAO, the greater the TNF-α.

Specific Aim 2. Examine the pro-inflammatory diet (DII), gut derived metabolite TMAO, and inflammation (TNF), with physical (HFSS) and depressive (CES-D) symptoms in heart failure patients while controlling for the related covariates. **H2a.** The greater the pro-inflammatory diet the higher physical and depressive symptoms. **H2b**. The greater the TMAO level the higher the physical and depressive symptom burden. **H2c**. The greater the TNF-α, the higher the HF physical and depressive symptoms.

Relevance and Background

Effective symptom control continues to be a significant priority in HF clinical care.[21] Management of symptoms involves a complete symptom assessment and adequate information to guide effective strategies to reduce symptom burden in HF.[24] Physical symptoms of heart failure, such as fatigue, listlessness, and trouble concentrating, often mimic depressive symptoms.[25] Psychological symptoms frequently go unnoticed or undertreated within the HF patient population, which leads to poor self-care and clinical outcomes.[26] Current literature suggests that depression rates increase with higher levels of HF severity, and rates ascend to 40-70% for HF patients in the acute care settings who are staged in NYHA class III-IV.[27] There have also been sex differences noted in disease severity, emotional response, and somatic complaints among men and women with HF.[25,27] Recent data indicate women may be more sensitive to inflammatory effects on behavior than men, indicating potential sex-specific differences in HF symptoms that deserve further investigation.[28] Additionally, Black adults have worse outcomes from HF and cardiovascular disease than other races with HF. Cardiovascular disease (CVD) risk factors such as hypertension and HF contribute to loss of life in Black adults at higher percentages than members of other races.[29] Black adults have an earlier onset of HF accompanied by a larger number of comorbidities (obesity, diabetes) which also contribute to symptoms.[29] Better understanding of the

underlying mechanisms associated with HF symptom burden is essential to develop future interventions. The findings of this study may lead to ways of identifying possible modifiable factors for symptoms in HF patients to inform future dietary intervention studies to improve outcomes in the HF population.

Symptom Burden, HF/Depression Link and Inflammation Systemic inflammation is a key pathophysiological process in the development and progression of HF, regardless of etiology.[6] A negative synergistic relationship exists between the physical symptoms and the emotional response to HF through biobehavioral pathways and HF. Pro-inflammatory cytokines may trigger specific symptoms of HF (e.g., malaise, fatigue, and loss of appetite).[26] Inflammatory diets derived from foods high in fat and carbohydrates may lead to exacerbation of heart failure severity and symptoms, and this highlights the biobehavioral pathway of diet and its potential connection to inflammatory processes in the body.[5,9,26] The pathological mechanisms linking symptoms and inflammatory cytokines, including TNF-α, in HF are poorly understood.[30] The link between cytokines and depression is a likely prognostic indicator in HF; it affects the quality of life and functional capacity of patients, thereby limiting their physical activity and decreasing chances of survival.[30] Current literature suggests psychological stress and depressive symptomatology may initiate the inflammatory response, solidifying links to the inflammatory process in physical exacerbations and depressive symptoms.[30,31] Social support is also important for its impact on reducing psychological symptoms.[32] With the existence of comorbid conditions, like obesity and low socialization resulting from depression in HF patients, symptoms can be especially burdensome. Studies seeking ways to alleviate this burden may be greatly beneficial for the well-being of this population.[30,33] Assessment of HF symptoms is varied, with studies focusing on one or more symptoms, symptom clusters, or overall symptom burden.[34] This study examines symptom burden as it provides a robust way to assess symptoms comprehensively with inclusion of frequency, severity, duration, and distress. Understanding the triggers and influencing factors of symptoms allows for precise intervention strategies.[33]

The multidimensional nature of this study will provide an innovative approach to addressing symptom needs in the HF population by examining a novel pathway linking dietary intake, overall

inflammatory diet, a specific gut derived metabolite (TMAO) which is generated from choline found in red meat, and symptoms. This research seeks to fill an important gap to clarify dietary and metabolic pathways that could be significant to individualized care and more precise symptom management.

Symptoms, Diet, TMAO, and Lifestyle Links There are several factors that may contribute to the symptom burden of HF patients, including inflammation,[35] diet type,[36] sex,[25] social support,[26] TMAO,[37] lifestyle factors,[38] and left ventricular ejection fraction.[39] Since HF is a condition with high symptom burden, dietary interventions have high promise to assist patients with symptom severity.[40] There is some preliminary evidence that HF outcomes have been linked to dietary patterns.[41] Recent findings suggest additional nutritional factors and modifications can greatly affect heart failure outcomes, and greater study is required to inform how dietary modifications can impact HF care.[37,41]

The **premise** of this study is that diet composition may influence HF outcomes and symptoms through a pro-inflammatory diet and a specific gut-derived metabolite that contributes to heart failure deterioration.[19,42] The gut-derived metabolite, TMAO, is metabolized mostly from two specific food components: phosphatidylcholine (choline) and L-carnitine (carnitine). Choline containing foods include eggs, steak, salmon, pork, and milk,[43] while carnitine containing foods include beef, fish, chicken, and milk.[44] Foods in these categories are highly reflective of what literature calls the "western diet", which was noted to be pro-inflammatory.[19] Notably, in healthy men and women, consumption of red meats leads to higher levels of TMAO in the blood.[37,45] TMAO is a key substance that may be derived from a pro-inflammatory diet and plays a role in the patient's disease severity.[14,15] TMAO also provokes a strong inflammatory response in blood vessels and contributes to negative CVD effects through thrombosis, inflammation, and chronic kidney disease.[18] This novel evidence warrants additional research for HF populations as most patients with HF have poor renal excretion and therefore more diet derived TMAO circulating in their bloodstream.[37] Thus, symptoms of HF may be affected by TMAO, the inflammatory cytokine TNF-α, and dietary intake.[8] The optimal diet for persons with HF remains unclear, and several controversies exist. Literature suggests that there are benefits with fish intake for those with cardiovascular disease. However, questions remain with dietary concerns in relation to TMAO; since fish

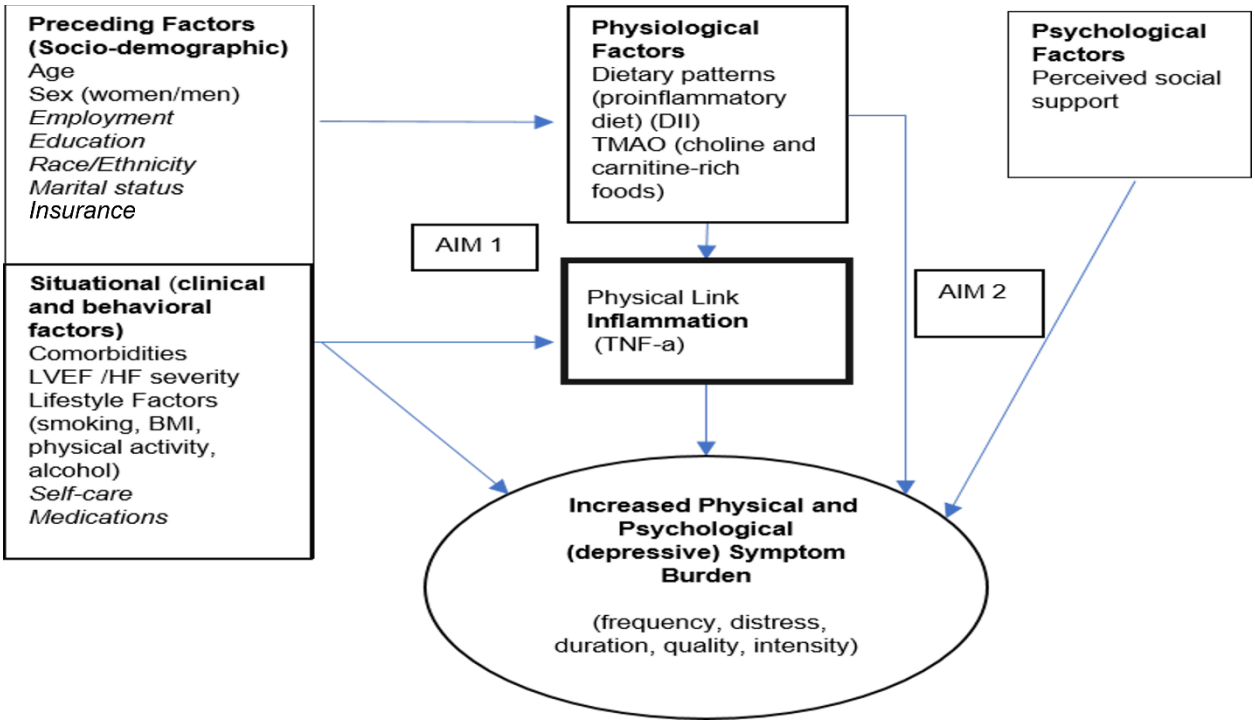
intake may involve increased TMAO blood levels, it may mean further complications with HF and outcomes.[46] Therefore, more focused examination of symptoms and specific metabolites from dietary intake is warranted to reconcile these controversies around heart healthy diets for HF patients. Thus, we examined *patterns* of inflammatory diets as well as TMAO versus examining only specific foods.

Although lifestyle factors, such as poor diet, low physical activity, smoking, alcohol intake, and excess caloric intake, are associated with worsening HF,[38,47,48] lifestyle attributes and modifications are under-utilized in the treatment and management of HF.[38] In fact, much of the cardiovascular research on lifestyle factors is focused on preventing HF rather than examining effective treatment approaches.[38,49] However, inflammation is implicated in many of the lifestyle factors mentioned above.[38,47,48,50] Therefore, we measured and controlled for these lifestyle factors in examining inflammatory dietary patterns and mechanisms of symptom burden. Factors affecting poor diet needed to be examined within the heart failure population; recommended dietary intake for HF patients is not well understood, and this may be contributing to prevalent issues within the HF community such as malnutrition, cachexia, and iron deficiency.[51,52] Additionally, pathophysiological changes may be occurring in HF patients that are not fully recognized during examination but are instantly reflected in symptoms.[26,53] This study was one of the first to link dietary inflammatory patterns as well as a gut-derived metabolite, a biomarker of inflammation, and depressive and physical symptoms in persons with HF to elucidate this modifiable pathway as a contributor to symptom burden. More knowledge in the area of symptom source and contributing factors can help health professionals potentially improve symptoms in HF patients based on their personal circumstances.[53]

Theoretical Framework and Conceptual Model

Figure 1.1 illustrates the theory-based conceptual model of the study with the solid lines representing variables to be controlled for in the analysis and words in italics representing notable variables to consider but not measured or controlled for in the study. The prospective study was grounded in a theory that frames the factors influencing symptoms through physiological, psychological, and social variables.

Figure 1.1. Theory Based Conceptual Model: Diet, Inflammation, and Symptom Burden for Persons with Heart Failure



Ultimately, the interconnected factors influencing several dimensions of the symptom experienced impact the functional and cognitive performance of the patient and potentially lead to poor quality of life and frequent rehospitalizations.[2] The Theory of Unpleasant Symptoms (TOUS) is a conceptual model that seeks to distinguish how multiple influential physiological, psychological, and social factors interact with symptom burden in a given population.[53]

Persons with heart failure often experience concurrent symptoms, and therefore preceding factors of these symptoms were explored. The TOUS provides a foundation for assessing these factors more coherently in the context of the individual's lifestyle. The sociodemographic factor of age is considered important in symptoms that may be related to inflammation.[54] Physiological factors that may impact heart failure symptoms are diet and related components such as TMAO and inflammatory patterns, ventricular function, and sex differences.[26,36,55,56] Since TMAO is preceded by inflammatory dietary factors and linked to decompensated heart failure and frequency of symptoms indicating worsening of the disease,[42]

increased TMAO was hypothesized to contribute to the development or triggering of physical symptoms. Psychological factors noted in this study were participants' perceived mechanism of social support.[27,32] Current studies directly link depression and the presence of a family member or caregiver as a proxy for social support to symptom burden.[32] Situational factors were defined as the individuals' medical status such as lifestyle factors, management of comorbidities, and other health related factors as listed above and demonstrated to be important for patient outcomes in the HF population.[38] The cross-sectional study focused on the various dimensions of symptoms and how the influencing factors interact with the symptoms thus clarifying the relationships and mechanisms linked to severity of heart failure and symptom presentation. The translational efforts of this study may lead to improved care plans for both registered nurses and providers and increase the capacity of health care providers to provide safe and individualized care.

Approach, Recruitment, and Study Sample

This proposal added an exploratory sub-study to a 2-year longitudinal observation study, currently in progress. The proposed sub-study was embedded in the parent study infrastructure as an observational cross-sectional study. In the parent study, funded as a P30 Pilot study (PI Brittany Butts) by the Emory Center for the Study of Symptom Science, Metabolomics, and Multiple Chronic Conditions (P30NR018090), 60 HF participants were to be recruited from the Centers of Heart Failure Therapy of Emory University Hospitals for the purpose of studying symptoms and metabolites. For this dissertation study, additional blood samples for TMAO and questionnaires (**Table 1.1**) were collected at baseline to measure variables to address the aims.

Sample: The targeted population in this dissertation study included self-identified Black (African, African American, and Afro-Caribbean) participants diagnosed with chronic HF and receiving optimal medical management, which may include combinations of angiotensin converting enzyme inhibitors, angiotensin II receptor blocking agents, beta blocking agents, and diuretics.[57] Participants with a New York Heart Association (NYHA) stage of II-IV were targeted for this sample. Inclusion criteria were: 30-80 years of age, and able to read, write, and understand English. Exclusion criteria were: the presence of

any of the following: severe chronic kidney disease as indicated by a glomerular filtration rate of less than 30 ml/min/1.73m^2 ,consented to hospice care, diagnosed with an uncontrolled mental disorder (i.e., schizophrenia, bipolar disorder, and major depression) as noted in medical records, receiving total parental nutrition or nutrition by a gastric tube, and uncontrolled severe hypertension (systolic >200 mmHg or diastolic >100 mmHg at baseline).

Setting: Participants were recruited from the HF clinics at Emory University and Emory University Midtown hospitals. Mentor Dr. Morris is a provider and active researcher in these sites and facilitated access to potential participants. The clinic calendar was used to identify HF patients scheduled to be seen in the Heart Failure Clinics. Patients were screened via the electronic medical record. A letter with a description of the goals and procedures of the study along with the risks of the study was sent to eligible patients to inquire if they are interested in participating in the study. Follow-up via telephone calls occurred one week after sending the recruitment letter.

Informed consent was obtained either via electronic informed consent using a secure REDCap link or via telephone, based on participant's preference and access to a computer or device with internet access. Participants who consented via telephone were allowed time for any questions they had regarding the study and the information provided on the consent form. Participants were asked to verify their understanding of the information regarding the study visit, which was virtual, including the number and time frame of the visits and the data collected at each visit. Participants who consented via electronic informed consent were provided with an orientation call to review expected data collection procedures and instructed to call or email the study team if they have any questions about the informed consent. Participants were instructed that should they agree to be in the study, they may withdraw at any time.

All data were collected remotely during the virtual study visit or in-person within the Wesley Woods Rehabilitation Center. A virtual or clinic visit (Zoom or telephone) was set up with a study team member to walk through the self-collection process. Participants were provided with a self-collection kit containing a Mitra micro-sampler kit with lancet for finger stick, written and pictorial instructions for self-collection; individuals with device and internet access were provided with a link to a video and a step-by-

step self-collection demonstration.[58] Each Mitra micro-sampler collects approximately 30 µL of capillary blood. Participants were also provided a return kit with pre-paid postage, a biospecimen bag with desiccant, and instructions for returning the self-collected samples and completed paper questionnaires. The nurse researcher obtained the specimens of participants for visits taking place in the Wesley Woods Center. Height was obtained via self-report, weight measured by the participant using their home scale. Scales were provided for those who did not have home scales. BMI was calculated with the following formula: (weight in kilograms)/(height in m)^2. Clinical variables, New York Heart Association (NYHA) Functional Classification, left ventricular ejection fraction (LVEF), and medications were collected from the electronic medical record. Co-morbidities were analyzed using the Charlson comorbidity index (CMI), developed to quantify risk of death from co-morbid diseases.[59] Questionnaires (**Table 1.1**) were made available via a REDcap link that was sent to participants via email to be completed on the day of the virtual visit. In addition, participants had the option to complete paper questionnaires, which were sent and returned with self-collection kits. All forms were reviewed for completeness upon receipt and participants were contacted for resolution of missing data, if any. Remuneration consisted of a fifty-dollar gift card, and a booklet of local support groups with essential community health resources related to heart failure care upon completion of the study.

The above procedures of data collection were tested with 3 participants of the parent study in a pilot to streamline procedures, and data collection was complete and acceptable including the self-collection and return of blood samples.

Screening and Lab Methods *(TMAO) and (TNF-α):* Blood for TMAO and TNF-α analyses were self-collected by participants using dried blood spots (DBS) obtained via Mitra micro-sampling.[60] DBS provided an easy to obtain, transport, and analyze remote collection blood source. Once returned to the research center, Mitra sponges were placed in 270 µl assay buffer (1x PBS + 0.05% TWEEN + protease inhibitor) in 2 mL LoBind microcentrifuge tubes and shaken at 550 rpm for 1 hour. This provided a total of 30 µL of working sample; up to 50 µL will be required for the TMAO assay. Extracted samples were stored at -80°C. Total protein will be quantified via Pierce™ 660nm Protein Assay Kit (ThermoFisher).

TMAO (BioHippo) and TNF-α (Olink®) levels were quantified using ELISA per manufacturer's instructions. Samples were analyzed in duplicate to ensure assay fidelity. TMAO analyses were performed by the study principal investigator (doctoral candidate) under the direct supervision of co-sponsor Dr. Butts.

Data Management and Analysis Plan

Data analyses were conducted using the latest version of SPSS 27; preliminary analyses examined variable distributions for normality, skewness, missing data, and outliers to determine if assumptions for statistical tests have been met. Bivariate correlations and linear regressions were examined for significance of the relationships with all outcome and predictor variables and the potential covariates (age, sex, comorbidities, lifestyle factor score, social support, LVEF). Aim 1 was analyzed with a series of bivariate correlations and multiple linear regression models to examine the DII in relation to TNF-α and TMAO, and the relationship between TMAO and TNF-α. For Aim 2, a full multiple linear regression model analysis was executed to examine relationships with the outcome variables (physical and depressive symptom scores) and with the independent variables of DII, TMAO, and TNF-α while also controlling for covariates. The best fit model was used to determine which independent variables contribute significantly to the dependent variable as designated in the aims. Effect sizes and p-values were noted along with the t-tests and chi-square differences for each group examined. Rationale for sample size: Given an expected sample size of 30 for a multiple regression model testing up to 1 predictor at a time and adjusting for up to 6 covariates at 80% power and 5% level of significance, the study was powered to detect a moderate-to-large effect size f2=0.29. Missing data was monitored throughout the research data collection procedures and the sociodemographic and preceding factors were analyzed by those with and without missing data. Corrections were applied as indicated in collaboration with the statistical mentor, Dr. Higgins. Data were corrected based on instructions for specific instruments that have more than 10% items missing.

Summary

The elements of this study are based upon the understanding of diet composition and how the inflammatory pathway may be useful in creating interventions to alleviate symptom burden in the HF population. The aims focused on exploring the nature of potential relationships thought to exist between an inflammatory marker (TNF-α), a diet-linked metabolite (TMAO), and a pro-inflammatory diet as measured by the dietary inflammatory index score (DII). This study was designed to illuminate the potential pathways linked to inflammation and TMAO through diet with symptom burden in a Black HF population.

Table 1.1 Variables and Measures

Variable and Measure	Description	Characteristics
Variable: Diet **Measure** Food Frequency Questionnaire 2014 with Block Analysis The Diet Inflammatory Index (DII) was calculated from the FFQ nutrient data.	12-category questionnaire that examines portion size, nutrient breakdown, and frequency of food types consumed.	The Cronbach's Alpha is between 0.61-.70. Validation studies completed with three-day dietary record and report acceptable results.[60] The DII is calculated using weights and a formula based on inflammatory foods consumed.[61]
Variable: HF Symptom Burden **Measure:** Heart Failure Symptom Survey	A 14-item self-report questionnaire to determine frequency, severity, interference with physical activity and enjoyment of life of HF symptoms. A total score is calculated.	Convergent and discriminative validity were established for this tool to verify its constructs. The Cronbach's alpha for this tool was measured between 0.80 and 0.88.[62]
Variable: Social Support **Measure:** Multidimensional Perceived Social Support Scale; MPSSS	A 12-item Likert survey assessing the patient's social support system with family and friends. Score is total of items.	The Cronbach's alpha was between 0.87-0.91. Validity was evaluated by comparing the results of this scale with other surveys such as the Hospital Anxiety and Depression scale. Convergent and factorial validity have been conducted to verify this scale.[63]
Variable: Sociodemographic and Clinical Data including comorbidity score and lifestyle score **Measure:** Common Data Elements, Charlson comorbidity index, and lifestyle inventory score (LIS).	Age, sex, race/ethnicity, education, employment & marital status, number in household, access to care, smoking status, socioeconomic stats, current medications, health history NYHA Class, LVEF, comorbidities.	A standardized sociodemographic and personal health history form included NINR BRICS variables and coding for demographics and comorbidity. (https://cde.nlm.nih.gov). The Charlson Comorbidity index was used as a covariate score. Kappa score 0.93. [64] The LIS is a brief questionnaire for patients used to collect information about smoking, drinking, obesity, and usual physical activity which is scored as a range with increasing scores for frequency of activity.[61]
Variable: Depressive Symptoms **Measure:** Center for Epidemiological Studies Depression Scale (CES-D) Short Form	A 10-item, self-report questionnaire that assesses symptoms of depression through mood, affect, and loneliness over 7 days.	The Cronbach's alpha is 0.88. Convergent and construct validity was performed for this instrument. Validity with this instrument has been established in ethnically diverse populations.[65]
Micro-sampling for gut-derived metabolite Trimethylamine-N-Oxide (TMAO) and inflammation biomarker (added for proposed study) TNF-alpha (TNF-α) *See lab methods	TMAO- DBS procedure TNF-α –DBS procedure	The Micro sampling procedure collects 30 μL dried blood spot (DBS) samples.

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Chapter 2

Heart Failure Symptom Burden, Dietary Intake, and Inflammation: A Review of the Literature

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Abstract

Background Heart Failure (HF) is characterized by high overall symptom burden including, but not limited to fatigue, dyspnea, and edema. Up to 21.5% of HF patients experience significant depressive symptoms, much higher than 7.1% in adults without HF. Diet, metabolites, and other inflammatory mechanisms have gained notable attention in recent studies for contributions to symptoms in HF. Symptoms for Black /African Americans (B/AAs) with HF are often influenced by lifestyle factors, which may influence their higher mortality rates; few studies address these factors. Distinguishing the links between key elements with diet, inflammation, and symptoms may bring clarity for new dietary strategies in HF clinical care.

Purpose The purpose of this integrative review is to examine the existing literature regarding relationships among physiologic pathways in HF along with physical and emotional symptoms in the context of inflammation, dietary intake, tumor necrosis factor (TNF-α,) a biomarker of inflammation, and trimethylamine-N-Oxide (TMAO).

Conclusions Based on available evidence, inflammation may be a key link between physical symptoms, diet, depression, TMAO, and TNF-α in persons with HF and warrants further examination to clarify pathological links to solidify evidence for better guidance with dietary modifications.

Clinical Implications The literature reviewed in this study demonstrates more work is needed to examine dietary planning, social support, and differences between men and women in the B/AA community. Results of this literature review call attention to the essential, personalized care needs related to symptom monitoring and dietary planning which is expected to decrease symptom burden in the HF population.

Key Words: Heart Failure, Inflammation, Depression, Symptoms, Diet

Introduction

Heart Failure (HF) cases in America have reached vast numbers with over 6 million individuals beyond the age of 20 years living with the condition.[1] Black or African American adults (B/AAs) have higher risks for HF due to increased rates of hypertension and cardiometabolic risk compared to the general population, have an earlier onset of HF, and have a 30-44% higher 5-year mortality rate as compared with other races.[2] Symptoms for B/AAs with HF are often influenced by social and behavioral factors, such as noncompliance with dietary guidelines based on cultural food preferences,[3] which may influence their higher mortality rates.[3] The existing literature notes that HF is one condition where dietary intake needs more attention, due to the risks associated with cachexia and malnutrition.[4] Diet not only affects outcomes in HF, but insufficient nutrients can have a direct negative effect on the pathophysiology of HF related to decreased cardiac function.[4] B/AAs have a cultural history of eating foods with high fat and carbohydrate content,[5] a diet that has been noted to be detrimental to the heart and contributing to high levels of inflammation.[6,7] This integrative literature review sought to examine the evidence of the relationships among HF symptoms, inflammation, diet composition, and the gut derived metabolite trimethylamine N-Oxide (TMAO) and other influencing factors. The focus is on the HF population in general with attention to the ethnic and cultural characteristics of the participants studied.

Background

Persons with HF often have nutritional imbalances, leading to electrolyte disturbances, cardiac insufficiency, and reduced functionality with impaired cardiac metabolism, all of which may affect physical HF symptoms such as fatigue and dyspnea.[8-10] For example, the increased intake of sodium in those with HF causes fluid retention and can lead to symptoms such as: fatigue, edema, and shortness of breath.[10] Some persons with HF lack the support needed to meet the needs of self-care through prescribed dietary recommendations to prevent adverse outcomes.[3] While there are gaps and discrepancies in the evidence that addresses dietary outcomes and specific interventions with HF patients, there is growing evidence supporting the need to integrate education about dietary composition and quality into HF care.[11]

Dietary composition in HF is important because certain nutrients and overall diet quality can impact HF patient outcomes and mortality.[11,12] Several studies affirm poor diet quality as a major modifiable lifestyle factor in the prevention of HF. However, the specific aspects of poor diet and mechanisms of action in HF outcomes are not well known. One theory is that a person's food intake may increase inflammation which in turn, would contribute to symptom burden. [10,13] Since HF has been recognized as a multi-system condition where inflammation has several pathways that cause injury and distress to the cardiac muscle, the intake of foods that may provoke a cytokine response may further lead to poor outcomes with increased symptoms; hence the recent studies that note the use of omega-3-fatty acids to decrease inflammation to aid against further damage in HF.[10,14] There have been several clinical and observational trials that provide evidence that the intake of fish and fish oils decreased mortality associated with ischemic heart disease.[14] An inflammatory diet has been recognized as a key contributor to cardiovascular disease, and examining diet quality among HF patients is essential to determine the best approach in maintaining an effective plan of care, especially with managing symptoms.[9] Inflammation has been linked to the incidence of HF, and studies suggest a pro-inflammatory diet may contribute to a multitude of somatic conditions, particularly obesity.[9,11] The pro-inflammatory diet may include foods such as red meat, highly sweetened foods, dairy products, and refined grains.[9] For persons with HF, nutritional intake has been shown to be important for quality of life and survival.[15] Therefore, food components, such as carnitine and choline, found in beef, pork, fish, and dairy products, are related to certain metabolites in HF and should be considered in the overall health and symptom management in this population.[16,17] Trimethylamine-N-oxide, (TMAO), derived from carnitine and choline, is one metabolite of interest in the HF population, as it has been found to influence severity of the disease due to inflammatory properties.[16,18-21] Tumor necrosis factor (TNF-α) is another inflammatory biomarker found to be significantly related to emotional and physical symptoms of HF patients.[22] This literature review will examine the relationships among physiologic pathways in HF and symptom burden in the context of inflammation, dietary intake, TNF-α, a biomarker of inflammation, and TMAO.

Methodology

This review covers a period starting from 2004 to the year 2021. Diverse search terms were used to elicit the articles reviewed, and all article types were considered from expert reviews, editorials, quantitative research studies, systematic reviews, and other integrative literature reviews. An overview of the steps and search terms for the integrative review conducted for this study is presented in Figure 2.1. The inclusion criteria for this study were as follows: experimental and non-experimental research literature discussing the key factors affecting HF patients in the context of symptom burden. Key variables were TMAO, nutrition and dietary studies related to HF patients, TNF-α, depression, and lifestyle factors (alcohol intake, physical activity, body mass index, and smoking). The electronic databases used for this study were PubMed and CINAHL and others as noted in Figure 2.1; peer-reviewed journal articles were sought out using four sets of key terms as listed in Figure 2.1. Using the identified search terms related to HF, lifestyle factors, TMAO, TNF-α, symptom burden, diet, Blacks, and inflammation, 132 articles were identified. The following exclusion criteria were applied to select the most relevant studies: duplicate articles, duplicate reported findings, non-HF populations with empirical studies, animal studies, dissertations, novels, non-English articles, qualitative studies, articles associated with congenital disease, and articles that were not related to the aim as previously mentioned. Articles that were updated over time with significant new insights were included for the study. Figure 2.1 delineates the process for which articles were excluded for this integrative review yielding a final set of 56 articles. Data analysis occurred through the subsequent detailed review of articles to note recurrent themes and patterns in the literature.[23]

Results

The results of this integrative review were organized into an evidence table that notes authors, year, citation, analysis, design, and outcomes/results (Table 2.1). The outcomes of the literature review were synthesized with the Theory of Unpleasant Symptoms to generate the model shown in Figure 2.2.[24] Multiple factors were found to influence physical and depressive symptoms of HF. The key areas

influencing outcomes in HF were diet, TMAO, inflammatory biomarkers, and depressive symptoms. Significant findings emerged throughout data analysis. Importantly, lower inflammatory markers were associated with lower HF symptoms.[25,26] TNF-α plays a key role in the development and exacerbation of HF and may serve as a modifiable target for lifestyle interventions .[27-30] Iron deficient persons with HF have increased levels of TNF-α in particular.[31] Factors that impact HF symptoms related to nutrition include socio-emotional factors, appetite/hunger, and illness related factors. The sickness behavior symptom cluster influences quality of life in a negative manner.[32] There is a strong connection among HF, depressive symptoms, and inflammatory symptoms, which have also been called sickness behaviors such as fatigue, malaise, and low appetite.[13,22,33] Depressive symptoms continue to be a key finding for each study with mood conditions in HF contributing to poorer outcomes and noted differences in depressive symptoms between men and women with HF.[34-37]

More themes of evidence included TMAO as contributing to mortality in the HF population, [38-40] and an unhealthy diet with lifestyle triggering inflammatory distress and even cardiac mortality with the ingestion of high carbohydrates and high fat meals.[39,41,42] TMAO was found to be influenced by diet and lifestyle especially with choline/carnitine rich dietary patterns.[43,44] In contrast, lower TMAO levels were related to improved outcomes in HF in terms of lower mortality rates.[21] Also, low sodium diets were linked to metabolite changes in persons with HF where there was improved energy utilization with carnitines and amino acids.[45] Many of the studies validated the significant role dietary patterns hold in the well-being or decline of persons with HF.[15,46-50] Furthermore, many of the articles presented chronic inflammation as a main contributor to depressive symptoms in HF, and sickness behaviors (fatigue, anhedonia, sleepiness) are present with depression in HF. [13,51] Additionally, ethnic differences were found between Asian and White HF populations in measured TMAO. Although higher levels of TMAO were found in Japanese populations, and elevated TMAO levels in White populations showed a greater association with morbid outcomes, little information has been found with TMAO and B/AAs. B/AAs were found to have dietary differences related to lower quantities of dietary antioxidants which were

linked to cardiac events.[43,52] An in-depth discussion of the relevant concepts to this review is expanded further in the sections to follow.

Discussion

Heart Failure Symptoms and Outcomes in the Black Population

While HF populations exist in every racial background, B/AAs appear to have a disproportionate prevalence of this disease along with worse outcomes.[53,54] The disparities seen in this population are directly related to the onset of this diagnosis, a larger number of risk factors, poorer long-term management, and multifaceted gaps of care involving social and environmental factors related to the individual.[54] Furthermore, depressive symptoms and reduced quality of life are prevalent in B/AAs, and about 60% of these individuals were found to be functionally impaired in a study examining ethnic variations of life quality and symptoms in decompensated HF.[55] In a study of B/AAs and White adults with HF, B/AAs were found to have a higher risk (OR 1.1,9) of readmission for chest pain than White adults.[56] Hospital readmission rates for B/AAs with HF are higher than White adults; ethnic variability must be considered in research to ensure more knowledge is available in how to best care for this population and reduce readmissions.[55]

One contributor to poorer outcomes in B/AAs of HF patients is thought to be dietary choices. The diet of B/AAs in the South contains a high intake of fried, salty, high-sugar, and processed foods.[5] In a study involving 383 B/AA women, dietary patterns were assessed to determine the interrelationship of food types with the incidence of obesity and chronic disease.[5] This study noted that B/AA women enrolled in a weight loss program were found to have low adherence to federal guidelines to diet and that women in this group did not follow dietary suggestions.[5] Although these women were found to have fruit, nut, and vegetable intake, they did not meet federal dietary guidelines, increasing risk for chronic diseases like HF.[5] Few studies have examined dietary intake in B/AAs with HF, and thus more research is needed

to better understand how cultural influences on eating habits relate to HF symptom outcomes. eating habits and relationship to their HF symptom outcomes.

Sociocultural influences on self-care have also been found to influence the symptom burden and outcomes of B/AAs with HF.[3] In Dickson's study of a B/AA HF cohort, members of this group struggled with aligning food preferences with medical guidelines that also accommodate their ethnic identity, social norms, and values.[3] These perceived discrepancies in dietary recommendations are a barrier to proper dietary management within this group.[3] This study further suggests that social support and cultural food preferences must be addressed when attending to matters of symptom recognition and management.[3]

Alleviation of symptoms in persons with HF is one of the core goals of nursing care and medical management.[57] Individuals living with HF often experience high levels of symptoms triggered by multiple factors including activity, diet, and other comorbidities ,and they may identify several symptom clusters throughout their course with the disease.[57] The physical symptoms of HF are often related to the depressive symptoms seen in this population.[57,58] Hospitalizations and readmissions in the HF population are often higher in the subgroup of patients that have been concurrently diagnosed with depression.[57] According to a study by Haedtke, et al., persons with HF who have co-morbid depression have a 57% increased rate of readmission.[57] The symptoms of depression in HF can easily mimic those of physical symptoms, such as fatigue, listlessness, and sleepiness;[13,57] together this symptom cluster has been identified as "sickness behaviors" and is well identified in literature as an outcome of those affected by HF and depression in particular.[13,58] Inflammation is thought to mediate symptom response and cardiac dysfunction in persons with HF. The mechanisms of inflammation have been identified in HF, and its links with depressive symptoms have been well documented.[13,59]

Inflammation and Heart Failure

Areas to consider when targeting inflammation in HF patients and alleviating symptom burden are diet and obesity, smoking, physical activity, and alcohol use.[11] Studies have shown that embracing a

diet high in fruit and vegetable intake, smoking cessation, increased physical activity, and moderate alcohol intake decrease the incidence of HF.[11,60] Thus, investigation of the role of healthy lifestyle factors in inflammation and symptom control of patients who have already been diagnosed with HF is warranted. Current literary evidence suggests lifestyle factors may be beneficial in preventing the advancement of HF in patients who carry a high burden of risks.[11] Although this may be a more effective approach for those with Stage A HF or pre-heart failure, the study suggests more research would be helpful in determining how this lifestyle management approach may succeed in those with more advanced stages of HF.[11]

There are few studies available in literature that examine modifying lifestyle factors to decrease inflammation in those with advancing stages of HF. Secondary prevention of HF after an acute event is under investigation, and studies to date examine physical activity, smoking, obesity management, and the effects of alcohol on those with later stages of HF.[61] These lifestyle factors have a common process which contributes to the development and exacerbation of HF: inflammation.[11] Studies have shown that the right dietary components, physical activity, and management of obesity can enhance the care plan for HF patients and combat the negative effects of inflammation which could increase the incidence of hypertension, atherosclerosis, and left ventricular remodeling, all of which promote advanced HF. [11] Smoking is also an identified risk factor linked to vascular inflammation and should be considered in the study of HF patients and symptom burden.[62] Alcohol intake poses yet another modifiable risk factor in preventing the continued inflammatory processes associated with HF exacerbations.[63] Alcoholic cardiomyopathy has been noted as a deterrent for promoting cardioprotective effects of alcohol, and HF patients are cautioned against habitual drinking.[11,63] B/AAs were noted in particular to have increased heart disease, coronary artery disease in specific, if moderate drinking was a part of their lifestyle.[63] Although alcohol has been linked with less vascular inflammation in the HF population, the amount of intake to maintain this favorable outcome does not appear to be clinically reliable.[64]

Inflammation, Depression, and Symptoms in Heart Failure

Inflammation in HF may be attributed to myocardial tissue injury and impaired cardiac function.[13] There were several studies that validate the interconnections between depression and HF via paths of inflammation with increasing cytokines in the blood.[13,59] Dekker examined the connections between depression and HF to better clarify how these two conditions exacerbate one another in terms of specific cytokines.[59] This study suggested that HF patients with depressive symptoms have shorter life expectancy and that inflammation may be the culprit for poor outcomes in the HF populations.[59] The Adamo study of inflammation and outcomes in the HF population provided evidence that the key pro-inflammatory cytokine present at higher levels in this population is TNF-α, in comparison with healthy groups.[65] In addition, immunological responses differed among patients having acute or chronic myocardial inflammation.[65] Many medical therapies are being examined to target inflammation in HF, and dietary approaches are being considered for this as well.[65,66]

Dietary Patterns, Sex Differences, and Inflammation

Nutritional modification in HF is considered a nonpharmacologic intervention.[67] Dietary fat, as well as general nutritional intake such as iron, may modulate the inflammatory processes and cytokines in HF.[31,66] Persons with HF who consumed more saturated and trans fats had higher levels of TNF-α in the blood.[66] Omega-3 fatty acids are a supplement of choice in the HF population as they have shown improvement in the blood levels of circulating cytokines.[10] Reducing the severity of inflammation in the HF population has shown to be a significant approach to care, and this may be done by examining foods consumed in this population to see where the changes need to occur.[10,66] Persons with HF need more guidance with dietary recommendations in terms of adequacy, potency, and portion sizes.[66] Such an approach to medical dieting for this population may complement a care regimen that aims to alleviate symptom burden as long as typical differences in food portions by sex are addressed.[68]

Several studies also highlighted the differences of HF symptom experience between men and women.[5,68] In a study by Vishram-Nielsen, women were found to have earlier onset of cardiac disease, more non-ischemic cardiomyopathy, lower jugular vein distension, and lower cardiac filling pressures than men.[69] Women were also more likely to have more symptoms than men with HF, had higher rates of obesity, had higher systolic blood pressure, higher heart rate, lower quality of life, and less comorbidities with the exception of hypertension.[70] In contrast, men and women have similar symptoms only when identified by clusters, with women experiencing higher distress because of the physical symptom burden in HF.[71] As the symptom experience may vary between the sexes, the impact of inflammation may be different as well as their dietary patterns.[71] While differences in symptoms by sex and differences in diet by sex have been reported, these interactions have not been fully explored.

The comparison of men and women with HF and general dietary intake is a significant topic within literature. One study asserts that men have higher overall food intake than women, were found to be less compliant with the low sodium diet plan, and also consumed meals with higher sodium density.[68] Another study provided evidence that men consume more energy density from the diet than women while women had a more beneficial dietary pattern overall with correlates for the self-determination index higher in women.[72] A study examining health behaviors between men and women found that women were more likely to avoid high fat foods, to consume fiber and more fruits, and reduce sodium intake in their diet.[73] Sex differences in dietary patterns becomes a significant topic for HF patients as the level of inflammation may be influenced by intake and therefore symptoms may also vary. Such knowledge and information may be helpful in determining how to best manage HF care and distinguish the triggers related to symptom burden.[10,12]

Trimethylamine-N-Oxide, Diet, and Heart Failure

Trimethylamine-N-oxide (TMAO) is a gut-derived metabolite that has been linked to inflammatory disease with HF, and thus is a potential link with symptom triggers in this condition.[16] Studies have shown that higher blood levels of TMAO were related to increased activation of

inflammatory genes and cytokines causing increased oxidative stress.[20] Furthermore, TMAO has been found to trigger other detrimental processes related to the heart such as thrombosis and platelet hyperactivity.[20] The key dietary components that are known to be precursors to TMAO are choline and carnitine; certain foods are metabolized into TMAO and have a significant part in the development of TMAO in the gut and bloodstream.[20] The studies show that humans consuming both meat and plant-based foods (omnivores) have higher TMAO levels than those who are vegans or vegetarians (herbivores).[20] The high-fat diet, also called the Western-Diet, has been linked to the increase of TMAO in blood in human research studies.[20] The overall effect of higher TMAO levels in the blood has been linked to mortality in patients with HF.[21] Available evidence currently suggests that dietary modification may be helpful in lowering TMAO levels in plasma.[21] In considering the consequences of inflammation in the HF disease process, TMAO is a central component that continues to be explored.[21] As for interventions in HF care, TMAO may need to be one of the core elements in managing symptom burden since it contributes to inflammation.[16,20,21]

Trimethylamine-N-oxide (TMAO), Dietary Elements, and HF Outcomes

With dietary patterns being an important consideration for the symptom management and outcomes in the HF population[12] as well as the recent scientific inquiry into TMAO and its link to inflammatory mechanisms with the heart, a deeper understanding of TMAO and its role in HF is needed. The majority of studies reviewed for this paper involved the gut derived metabolite, TMAO, the metabolite's link with the diet, and HF outcomes. Dietary composition is a key factor in the production of TMAO.[74,75] The nutrients choline and carnitine are found in many common foods consumed by the general population, including meat, eggs, and seafood products.[76] TMAO has gained much attention in the realm of scientific study, especially within the HF population, as it has been identified as a risk factor for the development of atherosclerosis as well as linked with poor outcomes with HF severity. [16,20,76] The metabolite TMAO has been explored to lessen the symptoms of HF and also promote greater outcomes in this population.[20] Literature suggests that TMAO triggers a proinflammatory pathway involving

cytokines, particularly TNF-α.[20] Higher levels of TMAO have also been found to increase the chances of a person developing a major cardiovascular event.[20]

HF outcomes may be linked to individual dietary intake.[77] As TMAO levels are associated with diet, dietary-associated TMAO may be a modifiable target for biobehavioral interventions to improve outcomes in persons with HF.[20] A study that examined chronic intake of red meats with a high fat diet and showed those with this intake had higher levels of TMAO in comparison to individuals consuming low fat diets or the Mediterranean Diet.[20] Fasting levels of TMAO were measured in a healthy adult population after a 6-month intervention with the Mediterranean diet and were not found to have significant change.[20] However, Yang, et. al. assert that TMAO levels in both plasma and urine may be influenced by lifestyle interventions involving exercise and a hypocaloric diet.[20] Even in pediatric populations, lifestyle interventions involving diet and physical activity were shown to have a positive effect on the percentage of TMAO levels in the body.[20] Lifestyle interventions, in particular, dietary changes for the HF population, will need to be further investigated to determine the influence of dietary modifications that reduce TMAO on symptoms and outcomes in the HF population.

No known studies to date have measured symptom burden from HF in relation to the TMAO levels or inflammatory measures like TNF-α. Many studies address the relationship between clinical disease severity, such as New York Heart Association (NYHA), of HF and the quantity of TMAO in the blood. In a study by Troseid, et. al, TMAO, choline, and betaine, two of its precursors, were examined in relation to inflammatory measures (c-reactive protein, CRP) and metabolic measures such as body mass index (BMI).[18] The end-point was all-cause mortality with anticipated mortality and identification of patients in need of heart transplants.[18] Results suggested elevated levels of TMAO, choline, and betaine are linked to increased disease severity, as indicated by NYHA, in HF. Another study examined the presence and quantity of TMAO in the plasma of acute HF patients, finding that patients with higher levels of TMAO had a more severe prognosis at 1 year and were predictive of mortality. [21] Thus, new treatment modalities that modulate TMAO in persons with HF may help improve outcomes, such as

emotional and HF physical symptoms, as several pathways linking dietary derived TMAO to inflammation may be amenable to dietary interventions.

Conclusion

The key aims of this literature review were to highlight symptom triggers and pathways linked to inflammation in the HF population in order to explore contributions of TMAO, dietary patterns, inflammatory biomarkers, and related factors of race, depression, sociocultural influences, and sex differences. Emerging knowledge within this literature review concluded that inflammation may be a key trigger of symptom burden in HF, and relationships between diet, depression, TMAO, TNF-α, and HF pathological processes must be further investigated to clarify pathological links and further solidify evidence to guide interventions. Additionally, this review illuminated the needs of the B/AA HF population related to dietary planning, social support, and sex differences in diet and HF symptoms. Results of this literature review call attention to the extensive pathways that may influence symptom burden in the HF population and focuses on our gaps in knowledge for future research to examine interconnections among TMAO, TNF-α, and dietary intake among persons with HF to improve their symptom experience.

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What's New:

- TNF-α plays a key role in the development and exacerbation of HF and may serve as a modifiable target endpoint for lifestyle intervention studies.
- TMAO was found to be linked to poor HF outcomes, inflammation, and is influenced by diets high in choline/carnitine.
- HF patients need specific, personalized guidance with dietary recommendations in terms of adequacy, potency, portion sizes, and attention to sociocultural dietary preferences.

Figure 2.1. Integrative Literature Review Methodology

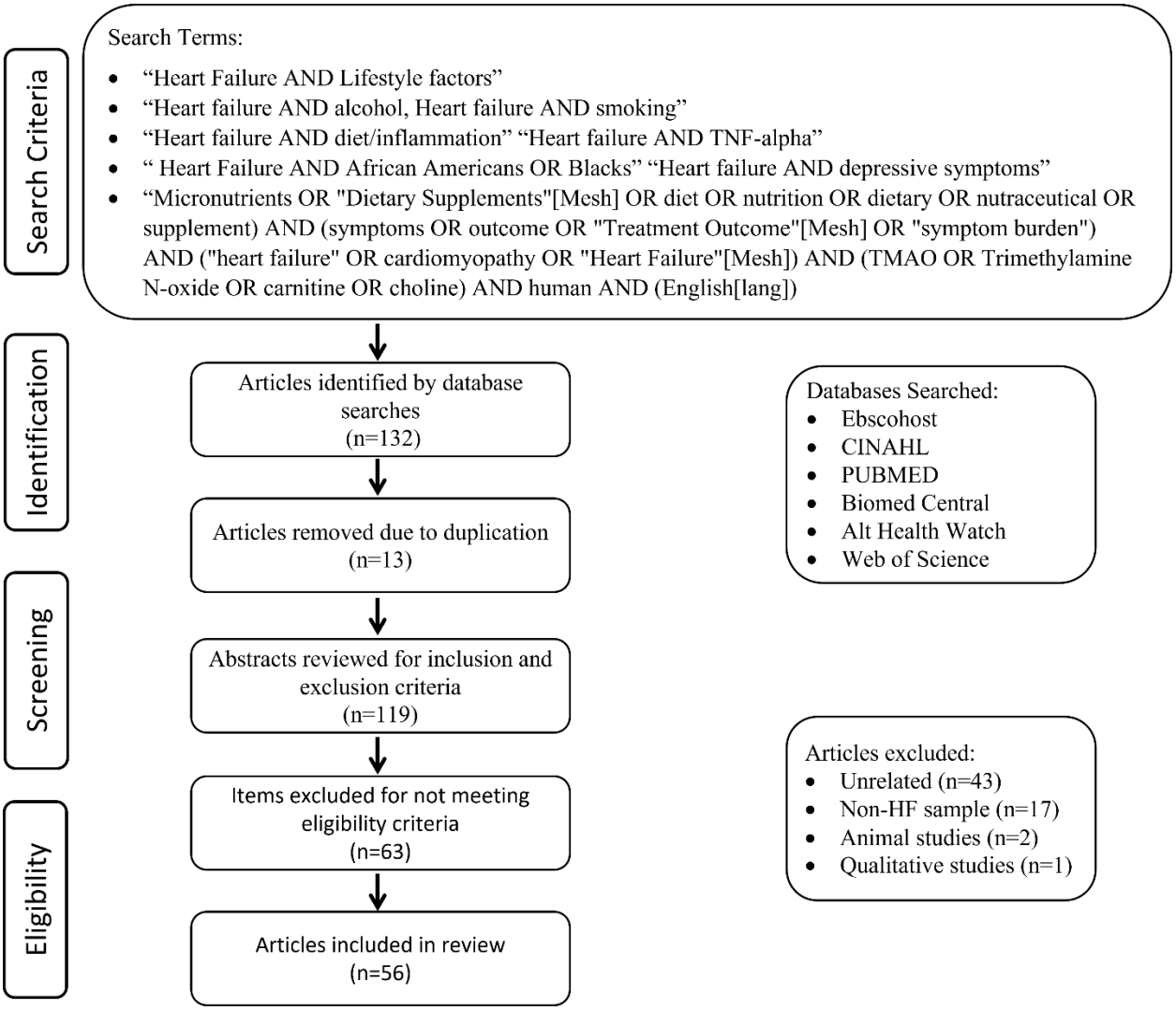

Figure 2.2. Theory Based Conceptual Model: Diet, Inflammation, and Symptom Burden for Heart Failure Patients

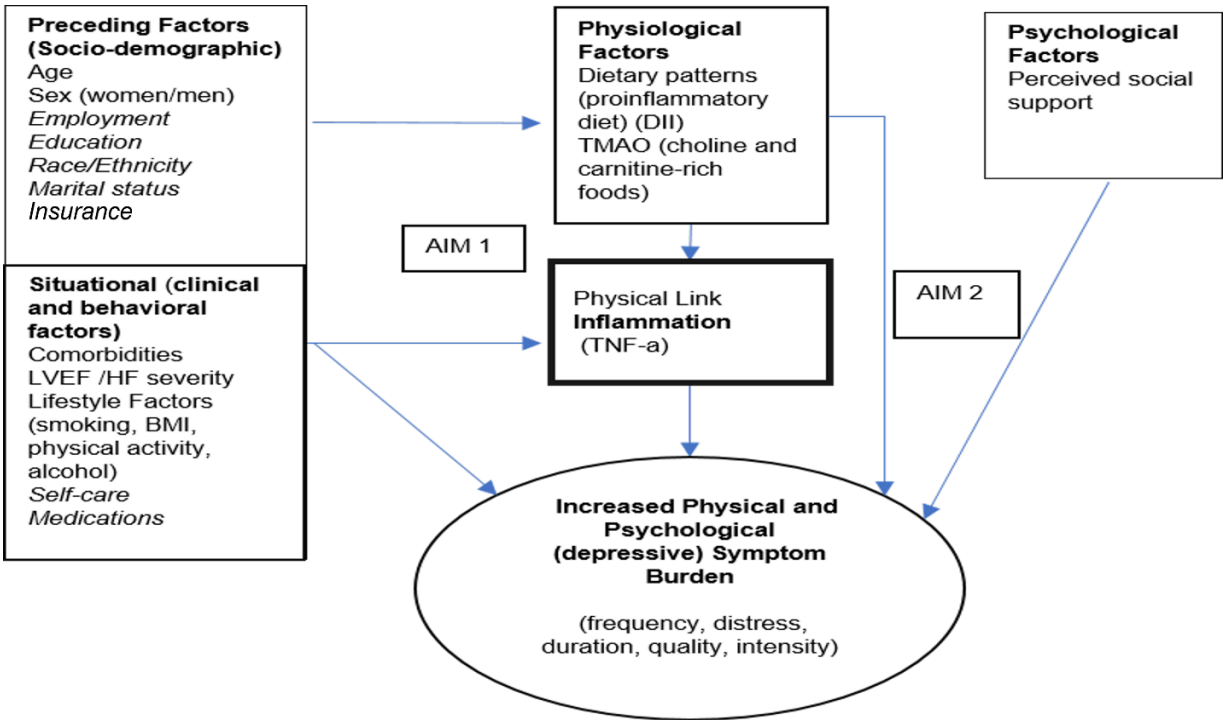

Table 2.1. Description of the Studies

Citation	Research Design	Sample and Setting	Analysis	Summarized results and key relationships
HF and Depressive Symptoms, Inflammation				
Heo S, Moser DK, Pressler SJ, Dunbar SB, Dekker RL, Lennie TA. Depressive symptoms and the relationship of inflammation to physical signs and symptoms in heart failure patients. *Am J Crit Care*. 2014;23(5):404-413. doi:10.4037/ajcc2014614	Prospective, observatory quantitative study	145 heart failure patients recruited over 5 years	Independent T tests and Chi-square tests	Patients with the lower levels of solid tumor necrosis factor receptor 1 (sTNFR1), a lower body mass index, less comorbidities, and more social support also had fewer physical symptoms of HF. sTNFR1 is sensitive to HF symptoms, there are a number of biomarkers, including TNF-α that are linked to HF symptoms, but more studies are needed.
Seongkum H, Moser DK, Pressler SJ, Dunbar SB, Dekker RL, Lennie TA. Depressive Symptoms and the Relationship of Inflammation to Physical Signs and Symptoms in Heart Failure Patients *American Journal of Critical Care.* 2014;23(5):404-413.	Prospective cohort study, cross-sectional.	145 HF patients were recruited from hospital-affiliated outpatient clinics.	Hierarchical multiple regression modeling, t-tests, and chi-square tests.	Depressive symptoms in HF should be considered a part of the physical symptom profile for these patients. Further studies are needed to examine the inflammatory pathway for the improvement of physical symptoms in HF in light of depressive symptoms.
Zahid I, Baig MA, Ahmed Gilani J, et al. Frequency and predictors of depression in congestive heart failure. *Indian heart journal.* 2018;70 Suppl 3:S199-s203.	Cross-sectional study	170 HF patients in tertiary care	Independent t-tests and chi-square tests	60% of HF patients were found to be depressed. Depression is higher in the HF population than it is the healthy

				population (by 3-fold). The progression of heart failure is linked to increased pro-inflammatory cytokines, which causes inflammation. TNF-α has a key role in the cause and development of HF.
Johansson P, Riegel B, Svensson E, et al. Sickness behavior in community-dwelling elderly: associations with impaired cardiac function and inflammation. *Biological research for nursing.* 2014;16(1):105-113.	Secondary analysis	415 HF patients in the community	Structural equation modeling, Mann-Whitney U test, Chi-square Test	Inflammation may accelerate the progression of HF and contribute to cardiac dysfunction. It is associated with poor prognosis. Inflammation and systolic dysfunction in HF are associated with anhedonia, fatigue, and sleepiness. Inflammation is linked to depression in patients with HF.
Haedtke CA, Moser DK, Pressler SJ, Chung ML, Wingate S, Goodlin SJ. Influence of depression and gender on symptom burden among patients with advanced heart failure: Insight from the pain assessment, incidence, and nature in heart failure study. *Heart & Lung.* 2019;48(3):201-207.	Retroactive, explanatory design (secondary analysis)	347 HF patients from outpatient clinics and home-based hospice programs	Descriptive statistics, t-tests, Mann-Whitney, and Chi-square tests were used for analysis, post-hoc analysis	The main symptoms found in this study were non-cardiac pain, dyspnea, and lack of energy. Patients with higher depressive scores displayed higher HF symptom burden. Deeper symptom assessment is needed to evaluate and treat high symptom burden in HF.
Salyer J, Flattery M, Lyon DE. Heart failure symptom clusters and quality of life. *Heart & Lung.* 2019;48(5):366-372.	Cross-sectional study	Convenience sample: 146 patients enrolled	Frequencies, multiple regression, and correlations	Factors that impact HF symptoms as related to nutrition include Socio-emotional factors, appetite/hunger, and

				illness related factors. The sickness behavior symptom cluster influenced quality of life in a negative manner.
van der Wal HH, Grote Beverborg N, Dickstein K, et al. Iron deficiency in worsening heart failure is associated with reduced estimated protein intake, fluid retention, inflammation, and antiplatelet use. *European heart journal.* 2019;40(44):3616-3625.	Secondary analysis	2357 HF patients in the database	Chi-square, mean, standard deviation, Mann-Whitney U, Logistic regression, and Kaplan Meier curves.	Iron deficient heart failure patients were found to have higher levels of inflammatory biomarkers and higher inflammatory states. Iron deficient HF patients have increased levels of TNF-α in particular. TNF-α directly impacts iron levels in HF patients.
Ferketich AK, Ferguson JP, Binkley PF. Depressive symptoms, and inflammation among heart failure patients. *Am Heart J.* 2005;150(1):132-136.	Primary analysis/cohort study	32 outpatient HF patients	Multiple linear regression	There was a significance between depression symptoms and TNF-α. There is a depression-based link with pro inflammatory cytokines that contributes to the mortality and morbidity.
Dewan P, Rørth R, Jhund PS, et al. Differential Impact of Heart Failure with Reduced Ejection Fraction on Men and Women. *Journal of the American College of Cardiology.* 2019;73(1):29-40.	Cohort Study	15,415 HF participants	Hazard ratios	Women had higher blood pressure, more obesity, higher heart rate. Women had higher emotional symptoms.
Vishram-Nielsen JKK, Deis T, Rossing K, Wolsk E, Alba AC, Gustafsson F. Clinical presentation and outcomes in women and men with advanced heart failure. *Scandinavian*	Retrospective study	429 HF patients	Kaplain-Meier, Cox-hazard analysis, log-rank tests.	Female survival rates were higher. Less deranged hemodynamics in women.

cardiovascular journal: SCJ. 2020;54(6):361-368.				
Sharma V, Zehtabchi S, Rojas N, et al. Ethnic variations in quality of life and depressive symptoms among Black Americans with acute decompensated heart failure. *Journal of the National Medical Association.* 2009;101(10):985-991.	Cohort Study	80% African Americans with HF	Univariate and multivariate analysis	Higher burden of depressive symptoms in HF led to higher prevalence of functional impairment.
Dekker RL, Moser DK, Tovar EG, et al. Depressive symptoms, and inflammatory biomarkers in patients with heart failure. *European journal of cardiovascular nursing: journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology.* 2014;13(5):444-450.	Secondary analysis/cohort study	428 HF patients in an HF registry	Multiple regressions	Depression has been found to impact mortality in HF. Inflammation was thought to be a predictor of worse outcomes in HF patients with depressive symptoms.
Lee KS, Song EK, Lennie TA, et al. Symptom clusters in men and women with heart failure and their impact on cardiac event-free survival. *The Journal of cardiovascular nursing.* 2010;25(4):263-272.	Cohort, prospective study	331 HF patients	Analysis of Variance, cluster analysis, chi-square, cox-proportional hazards	Symptom clusters to focus on were fatigue, sleep disturbances, dyspnea. Emotional and cognitive symptom clusters contributed to greater risk of cardiac events.
Angermann CE, Ertl G. Depression, Anxiety, and Cognitive Impairment: Comorbid Mental Health Disorders in Heart Failure. *Current heart failure reports.* 2018;15(6):398-410.	Literature review	NA	Review	There are many pathological mechanisms shared with emotional comorbidities with heart disease. Comorbid mood conditions in HF populations contribute to poorer outcomes.
Celano CM, Villegas AC, Albanese AM, Gaggin HK, Huffman JC. Depression and Anxiety in Heart Failure: A Review. *Harvard review of psychiatry.* 2018;26(4):175-184.	A literature review	NA	Review	Poor medical and functional outcomes have been linked to depression and anxiety in heart failure.

Murphy SP, Kakkar R, McCarthy CP, Januzzi JL, Jr. Inflammation in Heart Failure: JACC State-of-the-Art Review. *Journal of the American College of Cardiology.* 2020;75(11):1324-1340.	Expert literature review	NA	Review	Inflammation is key in the pathophysiology of heart failure/targeted for therapy. Sub-phenotypes should be considered for anti-inflammatory therapy with HF.
Alpert CM, Smith MA, Hummel SL, Hummel EK. Symptom burden in heart failure: assessment, impact on outcomes, and management. *Heart failure reviews.* 2017;22(1):25-39.	Literature review	NA	Review	Symptoms for patients with HF at the start of a hospital stay were not always improved by discharge. Unaddressed symptoms increase negative outcomes and reduce quality of life. Effective treatment for symptoms addresses more than the physical, but includes emotional, spiritual, and social effects of the suffering.
Chapa DW, Akintade B, Son H, et al. Pathophysiological relationships between heart failure and depression and anxiety. *Critical care nurse.* 2014;34(2):14-24; quiz 25.	Expert literature review	NA	Review	Pro-inflammatory cytokines may trigger specific symptoms of HF (i.e., malaise, fatigue, and loss of appetite) Depression contributes to greater mortality in HF. Pro-inflammatory cytokines are toxic to the heart and contribute to cardiac remodeling.

Shirazi LF, Bissett J, Romeo F, Mehta JL. Role of Inflammation in Heart Failure. *Current atherosclerosis reports.* 2017;19(6):27.	Expert literature review	NA	Literature Review	TNF- α can trigger cardiomyocyte disfunction and hypertrophy, fibrosis, and negative inotropic effects. High levels of TNF-α are linked to mortality. The measurement of biomarkers for inflammation may provide information on prognostics in heart failure. Cytokines are thought to be elevated in the state of heart disease.
Serafini M, Peluso Functional Foods for Health: The Interrelated Antioxidant and Anti-Inflammatory Role of Fruits, Vegetables, Herbs, Spices and Cocoa in Humans. *Current pharmaceutical design.* 2016;22(44):6701-6715.	Expert Review	NA	Literature Review	Inflammatory and oxidative stress can arise from an unhealthy dietary lifestyle with the ingestion of high fat and high carbohydrate meals. Diet can either induce or prevent inflammation.
Bordoni B, Marelli F, Morabito B, Sacconi B. Depression, and anxiety in patients with chronic heart failure. *Future cardiology.* 2018;14(2):115- 119.	Expert Review	NA	Literature Review	The pathological mechanisms linking symptoms and inflammatory cytokines, including TNF- α, in HF are poorly understood. The link between cytokines and depression is a likely prognostic indicator in HF; it affects the quality of life and functional capacity of patients, thereby limiting their physical activity and decreasing chances of survival.

Leonard BE. Inflammation and depression: a causal or coincidental link to the pathophysiology? *Acta neuropsychiatrica.* 2018;30(1):1-16.	Expert Review	NA	Literature Review	Chronic inflammation may contribute to depression. Sickness behaviors are present with depression and may also be distinct from it.
Siasos G, Tsigkou V, Kokkou E, et al. Smoking and atherosclerosis: mechanisms of disease and new therapeutic approaches. *Current medicinal chemistry.* 2014;21(34):3936-3948.	Literature Review	Review	NA	Smoking is also an identified risk factor linked to vascular inflammation and should be considered in the study of heart failure patients and symptom burden.
Diet, Symptoms, TMAO, Lifestyle				
Troseid M, Ueland T, Hov JR, et al. Microbiota-dependent metabolite trimethylamine-N-oxide is associated with disease severity and survival of patients with chronic heart failure. *Journal of internal medicine.* 2015;277(6):717-726.	Observational/prospective study	155 HF patients	Cox-regression and confidence intervals	TMAO levels were higher in patients with a higher stage of NYHA HF (III and IV). Associations with higher TMAO levels for ischemic HF patients were present. TMAO levels were not found to be correlated with LVEF.
Shivappa N, Godos J, Hébert JR, et al. Dietary Inflammatory Index and Cardiovascular Risk and Mortality-A Meta-Analysis. *Nutrients.* 2018;10(2).	Meta-analysis	HF study populations	Odds and hazards ratios, relative risks.	The pro-inflammatory diet is linked with increased CVD mortality.
Lourenço, B. H., Vieira, L. P., Macedo, A., Nakasato, M., Marucci Mde, F., & Bocchi, E. A. (2009). Nutritional status and adequacy of energy and nutrient intakes among heart failure patients. *Arq Bras Cardiol, 93*(5), 541-548. doi:10.1590/s0066-782x2009001100016	Prospective, observation study/cross-sectional study	125 outpatients with HF	Correlations to examine associations, non-paired t-tests, chi-square analyses, and Wilson-Signed ranked test.	HF patients displayed muscle depletion, poor nutrient intake, and inadequate energy stores. There is no link between dietary intake accounting for energy and nutritional status.

Suzuki T, Heaney LM, Bhandari SS, Jones DJ, Ng LL. Trimethylamine N-oxide and prognosis in acute heart failure. *Heart (British Cardiac Society).* 2016;102(11):841-848.	Observational cohort study	972 HF patients	Regression, Cox Analyses, descriptive statistics	TMAO levels were found to be a biomarker for death at 1 year. TMAO contributes to in-hospital mortality.
Song EK, Wu JR, Moser DK, Kang SM, Lennie TA. Vitamin D supplements reduce depressive symptoms and cardiac events in heart failure patients with moderate to severe depressive symptoms. *European journal of cardiovascular nursing : journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology.* 2018;17(3):207-216.	Cohort Study	177 HF patients	Linear and Cox Regressions	Vitamin D deficiency predicted more cardiac events.
Suzuki T, Yazaki Y, Voors AA, et al. Association with outcomes and response to treatment of trimethylamine N-oxide in heart failure: results from BIOSTAT-CHF. *European journal of heart failure.* 2019;21(7):877-886.	Secondary analysis	972 HF patients with worsening HF	Confidence intervals, hazard ratios	TMAO levels did not respond to guideline-based treatment with pharmacotherapy while those with high BNP levels did. Lower levels of TMAO showed better outcomes in HF patients.
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. *Journal of cardiac failure.* 2015;21(12):963-967.	Cohort study	13 hypertensive patients with HF	Logistic regression, correlations	Dietary changes with low sodium measures showed metabolite changes-improved energy utilization (among carnitines and amino acids.
Miró Ò, Estruch R, Martín-Sánchez FJ, et al. Adherence to Mediterranean Diet and All-Cause Mortality After an Episode of Acute Heart Failure: Results of	Prospective cohort study	991 patients	Confidence intervals and hazard ratios.	The Mediterranean diet was linked to decreased rates of hospitalization. Although not correlated with long-term mortality.

the MEDIT-AHF Study. *JACC Heart failure.* 2018;6(1):52-62.				
Lennie TA, Chung ML, Habash DL, Moser DK. Dietary fat intake and proinflammatory cytokine levels in patients with heart failure. *Journal of cardiac failure.* 2005;11(8):613-618.	Prospective cohort study	42 HF patients	Kaplain-Meier methods and survival curves	The more the inflammation the less survival in the HF population. Cardiac-event free survival was reduced in patients with higher TNF-α and sTNF-R1 levels. Dietary fat may impact proinflammatory cytokine levels in patients with HF.
Eastwood JA, Moser DK, Riegel BJ, et al. Commonalities and differences in correlates of depressive symptoms in men and women with heart failure. *European journal of cardiovascular nursing : journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology.* 2012;11(3):356-365.	Secondary analysis from the Heart Failure health related quality of life registry	622 heart failure patients, adults 18 and over	ANOVA analyses and Chi-square models	Depressive symptoms in men and women were different in the context of HF. Reducing depressive symptoms in HF patients may require gender-based risk profiles. Weight management needs to be addressed with women, functional capacity for men. Men and women may need to have anxiety and perception of control addressed.
Lennie TA, Moser DK, Chung ML. Insight Into Differences in Dietary Sodium Adherence Between Men and Women With Heart Failure. *The Journal of cardiovascular nursing.* 2020;35(2):131-136.	Cohort, prospective study	223 HF patients	T-tests and Chi-squares	Dietary differences exist between men and women. Men consume more food. Greater attention should be given to food quantity and type.
Heianza Y, Ma W, Manson JE, Rexrode KM, Qi L. Gut Microbiota	Meta-analysis and expert review.	Review of prospective studies with	Confidence intervals and relative risks	TMAO, in higher concentrations of

Metabolites and Risk of Major Adverse Cardiovascular Disease Events and Death: A Systematic Review and Meta-Analysis of Prospective Studies. *Journal of the American Heart Association.* 2017;6(7).		cardiac populations		the blood is linked to cardiac events. Increased intake of phosphatidylcholine is linked with more CVD risk/mortality. Increased TMAO contributes to atherosclerosis.
Wu JR, Song EK, Moser DK, Lennie TA. Racial differences in dietary antioxidant intake and cardiac event-free survival in patients with heart failure. *European journal of cardiovascular nursing : journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology.* 2018;17(4):305-313.	Secondary analysis	247 African American HF patients	Cox Regression Analysis	African American patients had more diets with less antioxidants. Antioxidant diets are linked to more cardiac event-free survival.
Kumar A, Singh RB, Saxena M, et al. Effect of carni Q-gel (ubiquinol and carnitine) on cytokines in patients with heart failure in the Tishcon study.	Randomized controlled trial	62 HF patients	Analysis of Variance and Chi Square Tests	Feasibility for treatment of HF inflammation was tested with a dietary intervention (carnitine and ubiquitol) and found less pro-inflammatory cytokines in circulation-including TNF-α.
Yazaki Y, Aizawa K, Israr MZ, et al. Ethnic differences in association of outcomes with trimethylamine N-oxide in acute heart failure patients. *ESC heart failure.* 2020.	Cohort study	1087 HF patients from Caucasian, Asian populations	Mann-Whitney U, Cox regression, Chi-square tests	TMAO is impacted by diet and lifestyle, with choline and carnitine rich dietary patterns. Cultural and ethnic differences in diet must be examined further in HF populations.
Zinöcker MK, Lindseth IA. The Western Diet-Microbiome-Host Interaction and Its Role in Metabolic Disease. *Nutrients*. 2018;10(3):365. Published	Expert literature review	Literature review	NA	The Western diet is linked to inflammation that is derived from structural and behavioral changes

2018 Mar 17. doi:10.3390/nu10030365				in the resident microbiome.
Bianchi VE. Impact of Nutrition on Cardiovascular Function. *Current problems in cardiology.* 2020;45(1):100391.	Review of the literature	Review	NA	For Chronic HF patients, diet is important for improvement of life quality and survival. Ischemic HF patients' low oxygen availability and the use of glucose must increase.
Ufnal M, Nowiński A. Is increased plasma TMAO a compensatory response to hydrostatic and osmotic stress in cardiovascular diseases? *Medical hypotheses.* 2019;130:109271.	Review of literature	Review	NA	TMAO has a negative impact on cardiac events and coronary artery events.
Freedland KE. Diet, Depression, and Destiny in Heart Failure. *Journal of cardiac failure.* 2015;21(12):952-953.	Editorial-expert report	NA	NA	Patients with high symptom burden and functional impairment may need nutritional and mental support services, both to improve their quality of life and to help to reduce their risk of mortality.
Butler T. Dietary management of heart failure: room for improvement? *Br J Nutr.* 2016;115(7):1202-1217.	Expert Review	Review	NA	There are lacking data and guidelines for diet in HF patients. Cardioprotective fats need to be evaluated in HF. Other dietary components need to be explored rather than just sodium and potassium.
Abshire M, Xu J, Baptiste D, et al. Nutritional Interventions in Heart Failure: A Systematic Review of the Literature.	Literature review	Review	NA	Providing education for nutritional interventions in heart failure positively affect

Journal of cardiac failure. 2015;21(12):989-999.				A low sodium diet may be harmful for HF populations.
Rea IM, Gibson DS, McGilligan V, McNerlan SE, Alexander HD, Ross OA. Age and Age-Related Diseases: Role of Inflammation Triggers and Cytokines. *Frontiers in immunology.* 2018;9:586.	Literature review	Review	NA	TNF-α was found to be elevated in post-heart attack patients and increased the risk of reoccurring cardiac disease.
Rahman A, Jafry S, Jeejeebhoy K, Nagpal AD, Pisani B, Agarwala R. Malnutrition and Cachexia in Heart Failure. *JPEN Journal of parenteral and enteral nutrition.* 2016;40(4):475-486.	Expert review	Review	NA	Cachexin/TNF-α is a noteworthy biomarker in HF disease process. Vitamin D deficiency is associated with worser outcomes in HF.
Jia Q, Li H, Zhou H, et al. Role and Effective Therapeutic Target of Gut Microbiota in Heart Failure. Cardiovasc Ther. 92019::5164298-5164298.	Literary review/ summary	Review	NA	TMAO levels are higher in HF patients as compared with healthy populations, linked to NYHA grades, ischemic HF, and morbid outcomes.
Lennie TA, Moser DK, Biddle MJ, et al. Nutrition intervention to decrease symptoms in patients with advanced heart failure. *Res Nurs Health.* 2013;36(2):120-145.	Expert review /proposal	Proposed 175 patients with advanced HF	Proposed-mixed methods with randomized trial	Evidence suggests that symptoms and nutrition have a positive correlation, nutrition could have a key role for outcomes and symptoms in HF. Decreasing the cytokine response in HF is a strong target for improving symptoms.
Yang S, Li X, Yang F, et al. Gut Microbiota-Dependent Marker TMAO in Promoting Cardiovascular Disease: Inflammation Mechanism, Clinical Prognostic, and Potential as a Therapeutic Target. *Frontiers in*	Summary of clinical evidence	Review of clinical studies	NA	TMAO is linked with both inflammation and inflammatory biomarkers, including TNF-α.

pharmacology. 2019; 10:1360.				
Kuehneman T, Gregory M, de Waal D, et al. Academy of Nutrition and Dietetics Evidence-Based Practice Guideline for the Management of Heart Failure in Adults. *Journal of the Academy of Nutrition & Dietetics.* 2018;118(12):2331-2345.	Summarized review of the literature for expert work	Review	NA	Nutrition in the treatment of HF is considered a non-pharmacological intervention. Optimal nutritional management can reduce admissions and mortality.
Kerley CP. Nutritional Interventions in Heart Failure: Challenges and Opportunities. *Current heart failure reports.* 2018;15(3):131-140.	Expert literature review	Review	NA	There's evidence that those following either the DASH or Mediterranean diet had reduced HF. Low-fat and plant-based diet showed improved ejection fraction and cardiac biomarkers.
Kerley CP. Dietary patterns and components to prevent and treat heart failure: a comprehensive review of human studies. *Nutrition research reviews.* 2019;32(1):1-27.	Expert literature review	Review	NA	Red meats, processed meats, carbohydrates are harmful for HF patients/fish and poultry remain controversial. Bioavailability and inflammatory mechanisms must be considered with diet and HF patients.
Aggarwal M, Bozkurt B, Panjrath G, et al. Lifestyle Modifications for Preventing and Treating Heart Failure. *Journal of the American College of Cardiology.* 2018;72(19):2391-2405.	Expert literature review	Review	NA	Diets high in red meat may increase inflammation. The incidence of HF has been correlated with inflammation.
Payne-Emerson H, Lennie TA. Nutritional considerations in heart failure. *The Nursing clinics of North America.* 2008;43(1):117-132; vii.	Expert review	Review of guidelines in heart failure	NA	Inflammation influences nutrition requirements in HF. Dietary fat affects the inflammation process in HF.
Rohde LE, Beck-da-Silva L. SecoAlcohol and the heart: the good, the bad	Editorial Review	Evidence review	NA	Alcoholic cardiomyopathy has been noted as a

and the worse in heart failure. *Heart (British Cardiac Society).* 2018;104(20):1641-1642.				deterrent for promoting any cardioprotective effects of alcohol and heart failure patients should be especially cautious with engaging with habitual drinking.
Tang WHW, Li DY, Hazen SL. Dietary metabolism, the gut microbiome, and heart failure. *Nature reviews Cardiology.* 2019;16(3):137-154	Literature Review	Review	NA	Patients in the highest quartile of TMAO had a greater risk for heart attack, stroke, or death. Fish oil may hinder the harmful effects of TMAO. Those with high TMAO levels and are at risk for retaining it are instructed to reduce their protein intake.

Chapter 3

Relationships between The Western Diet and Inflammatory Mechanisms in Persons with Heart Failure

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Abstract

Introduction Black individuals have a higher risk for heart failure (HF) than other race and ethnic groups, which is thought to be due, in part, to higher prevalence of traditional cardiovascular risk factors. The Western Diet (WD) is associated with increased burden of cardiovascular (CV) risk factors and plays a role in the pathophysiology of heart failure (HF). Trimethylamine-N-oxide (TMAO) is a diet-linked metabolite that contributes to inflammation and is associated with higher levels of tumor necrosis factor (TNF)-α, especially in HF populations. The dietary inflammatory index (DII) score measures the inflammatory potential of a diet and the inflammatory effects of foods. More studies are needed to determine how the WD impacts immunological pathways and cytokines in the context of clinical and population characteristics.

Purpose The aim of this study was to explore associations between the WD, DII, TMAO, and TNF-α in Black adults living with HF.

Methods Thirty-one self-identified Black participants (mean age 55.3, 67.7% women) with HF were enrolled. TMAO and TNF-α levels were analyzed from blood spots using immunoassays. Participants completed a Food Frequency Questionnaire (FFQ), from which a DII score was calculated. Food groups and nutrients, like choline, were measured with the FFQ. Analyses included correlational and inferential statistics.

Results Mean DII score was -.38, revealing an overall anti-inflammatory diet with higher inflammatory scores among men (-.23) as compared to women (-.43). Women consumed greater kilocalories with more saturated fat, sodium, dairy, sugar, and fruit while men consumed more cholesterol, choline, proteins, alcohol, legumes, poultry, red meats, eggs, and phosphatidylcholine. DII score was negatively correlated with dietary choline ($r=-.73$, $p<.001$), but did not correlate with TMAO or TNF-α. TNF-α and TMAO were positively related ($r=.277$, $p=.138$).

Conclusions In patients with HF, it is important to monitor intake of inflammatory foods and appreciate that increasing age may play a role in the retention of dietary metabolites. This sample of HF patients from a busy HF referral center did not consume a highly pro-inflammatory diet, yet our findings provide insight for specific food groups such as those with choline. Further study of these relationships in patients with HF could lead to tailored dietary educational interventions based on dietary patterns, age, and cultural relevance.

Key Words: Heart Failure, Diet, Inflammation

Introduction and Background

The typical Western Diet (WD) consists of a dietary pattern characterized by refined sugars, processed meats, white flour, salts, animal fats, and food additives, while containing low amounts of vitamins, minerals, antioxidants, and fiber (Christ et al., 2019). The WD is known to produce a high glycemic index and is generally not considered a balanced diet but one that promotes weight gain (Napier et al., 2019). Furthermore, the WD has been linked to higher serum indicators for inflammation, and this immune response is potentially a direct result of the WD consumption (Christ et al., 2019). Some human studies suggest the WD can influence chronic inflammation and inflammatory diseases, but there is little evidence to determine exactly how the WD influences immunological pathways and thereby the outcome of an inflammatory disease like heart failure (HF) (Napier et. al., 2019).

Diet-related diseases have often been linked to the WD, and the culture of any population with HF should be examined in relation to the food patterns they consume for this reason (Zinöcker & Lindseth, 2018). The dietary culture of Black or African American adults (B/AAs), contributes to obesity among other chronic conditions, particularly among women (Sterling et al., 2018). B/AAs living in the South experience obesity disproportionately, and consumption of a Southern-style diet may further increase obesity risk. A typical Southern style diet may include, but is not limited to, a higher intake of salted and fried foods, foods that are highly sweetened, and red processed meats (Sterling et al., 2018). Even from an early age, B/AA children may be at a greater risk for obesity and cardiovascular disease because of the dietary patterns during childhood with the consumption of salty snacks, high-sugar beverages, and insufficient intake of fresh vegetables and grains (Doswell et al., 2018). With this background, B/AAs have a higher risk of early onset HF and have increased risk of adverse clinical outcomes compared to other racial and ethnic groups. Thus, greater efforts towards earlier detection of HF should be facilitated (Lekavich & Barksdale, 2016). Inflammation that advances HF severity could be linked to dietary intake and should be explored in HF patients. The connection between a WD or Southern

diet should be examined as a potential mechanism to prevent future HF exacerbations (Murphy et al., 2020).

The role of dietary intake in HF has long been recognized as an area of opportunity for the improvement of HF management among scientists and clinicians (Lennie et al., 2005). There is evidence that dietary fat intake increases the level of proinflammatory cytokines linked to the progression of HF, including tumor necrosis factor (TNF)-α (Lennie et al., 2005). TNF-α has been found to be consistently elevated and associated with decreased survival in persons with HF (Lennie et al., 2005). Targeting the inflammatory pathway in persons with HF may promote better understanding of mechanisms related to the pathophysiology of HF, especially those specific to the diet. In addition to TNF-α, trimethylamine-N-oxide (TMAO) is a gut-derived metabolite that has been linked to reduced function of the heart (Heianza et al., 2017). TMAO contributes to cardiac dysfunction via pro-inflammatory endothelial cell activation (Heianza et al., 2017). TMAO is noted to be diet-linked as its constituents are found in many of the foods identified in the WD such as red meat, eggs, and shellfish (Yang et al., 2019). The inflammatory process triggered with TNF-α in HF and the inflammatory contributions of TMAO together present a combined pathway that may be driven by dietary intake (Yang et al., 2019). The aims of this study are to examine the links between the pro-inflammatory WD and levels of TMAO and TNF-α and to examine the relationship between TNF-α and the metabolite TMAO. Figure 3.1 presents a model based on current studies evaluating the suspected effects of TMAO and TNF- α on the heart in relation to dietary intake. In evaluating these potential relationships, clarity may be gained regarding the inflammatory response in HF, and thereby lead to greater knowledge of targeted dietary therapies and prognosis of HF.

Methods

Research Design

This observational, cross-sectional study involved 31 participants with a diagnosis of HF recruited from the Center for Heart Failure Therapy at the Emory University Hospital outpatient clinic.

The targeted population in this study included self-identified B/AA (African, African American, and Afro-Caribbean) participants diagnosed with chronic HF and receiving optimal medical management, which at the time of this study included combinations of angiotensin converting enzyme inhibitors, angiotensin II receptor blocking agents, beta blocking agents, mineralocorticoid receptor antagonists, hydralazine and isosorbide dinitrate, and diuretics (Yancy et al., 2017). Inclusion criteria are: 30-80 years of age and able to read, write, and understand English. Exclusion criteria are the presence of any of the following: severe chronic kidney disease, defined by an estimated glomerular filtration rate of <30 ml/min/1.73m^2, consented to hospice care, diagnosed with an uncontrolled mental disorder (i.e., schizophrenia, bipolar disorder, and major depression) as noted in medical records, receiving total parental nutrition or nutrition by a gastric tube, and uncontrolled severe hypertension (systolic >200 mmHg or diastolic >100 mmHg at baseline). The study was approved by the Institutional Review Board as a sub-study of its parent study *Metabolomic Pathways to Fatigue, Depression, Anxiety, and Dyspnea in Black Adults with Heart Failure and Hypertension* (Butts et al., 2022).

Data Collection and Lab Procedures

Study data were collected and managed using REDCap electronic data capture tools hosted at Emory University. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources (Harris et al., 2009), (Harris et al., 2019). Informed consent was obtained either by electronic means using a secure REDCap link or via telephone, based on participant preference and access to a computer or device with internet access. Clinical variables left ventricular ejection fraction (LVEF), and medications were collected from the electronic medical record. Co-morbidities were analyzed using a weighted score of the Charlson comorbidity index (CCI), developed to quantify risk of death from co-morbid diseases (Charlson et al., 1987). The Food Frequency

Questionnaire (FFQ) was made available via an electronic link that was sent to participants via email to be completed on the day of the virtual visit. Forms were reviewed for completeness upon receipt and participants were contacted for resolution of missing data, if any. The 2014 version of the Food Frequency Questionnaire was utilized for dietary data collection (Fatihah et al., 2015). The Dietary Inflammatory Index (DII) score was used in conjunction with the FFQ to calculate scores representing the level of inflammation as denoted by inflammatory cytokines like TNF-α (Shivappa et al., 2014). Lifestyle factors were also assessed by self-report as to whether individuals smoked, used alcohol, exercised for at least 150 minutes per week, or had a body mass index (BMI) of 30 kg/m^2 or higher. The higher the lifestyle score the greater their risk for symptom burden (Aggarwal et al., 2018). Sociodemographic variables, age, and sex were collected to display the sample characteristics.

Blood for TMAO and TNF-α analyses was self-collected by participants using dried blood spots (DBS) obtained via Mitra micro-sampling, as previously described (Butts et al., 2022). Mitra sponges (30 µl) were placed in 270 µl assay buffer (1x PBS + 0.05% TWEEN + protease inhibitor) and shaken at 550 rpm for 1 hour. Extracted samples were stored at -80°C. Total protein was quantified via Pierce™ 660nm Protein Assay Kit (ThermoFisher). TMAO (BioHippo) was quantified using ELISA per manufacturer's instructions. TNF-α was analyzed via multiplex immunoassay (Olink®). Samples were analyzed in duplicate to ensure assay fidelity.

Statistical Analyses

Data analyses were conducted with SPSS 27 software (IBM, 2020); preliminary analyses examined variable distributions for normality, skewness, missing data, and outliers to determine if assumptions for statistical tests were met. Bivariate correlations and linear regressions examined the significance of the relationships with all outcome and predictor variables and the potential covariates (age, sex, comorbidities, lifestyle factor score, LVEF). The main research aim was analyzed with a series of bivariate correlations and multiple linear regression models to examine the dietary inflammatory index (DII) in relation to TNF-α and TMAO, and the relationship between TMAO and TNF-α. Given a

sample size of 30 for a multiple regression model testing up to 1 predictor at a time and adjusting for up to 6 covariates at 80% power and 5% level of significance, we were powered to detect a moderate-to-large effect size f2=0.29.Results with moderate to large effect sizes were reported regardless of p-value (Andrade, 2019). For the variables that were skewed, Spearman correlations were performed. Tests for multicollinearity were performed, and there were no issues noted.

Results

A total of 31 participants were recruited for this observational study with 6 variables examined in relation to the outcome variables. The mean age was 55.3 ± 12.2 years, and 67.7% were female (Table 3.1.) The mean total DII score was -0.38, mean TMAO was 6.46 ng/ml, and mean TNF-α was 1.65 pg/ml (Table 3.2). TMAO was examined accounting for creatinine levels as a proxy of renal function. After accounting for sex, creatinine was not found to be associated with TMAO. TMAO was not found to have a significant relationship with betaine, total choline, or phosphatidylcholine in the diet or omega-3-fatty acids. Dietary choline was negatively correlated with total DII score ($r= -0.73$, $p<.001$).

There were no correlations found between DII score and TMAO or TNF-α. TNF-α was positively related to TMAO ($r=0.277$, $p=0.138$; Figure 3.2). In an unadjusted regression model, as well as an adjusted regression model adjusting for age, sex, comorbidities, lifestyle factors, and LVEF was performed to examine the relationships between DII, TNF-α, and TMAO. There were no significant findings in the unadjusted or adjusted regression models for TMAO as a dependent variable, nor DII or TNF-α as dependent variables. Each regression procedure was also performed with TMAO and DII as predictors and adjusted for the 5 covariates aforementioned. No significant findings were found. However, DII was negatively correlated with LIS ($r=-0.49$, $p=0.010$). Total DII score was also negatively correlated with choline from phosphatidylcholine ($r=-43$, $p=0.033$).

There were no significant correlations found with TMAO and poultry, red meat, eggs and dairy, or fish; these food groups have been found to contain excessive amounts of choline and carnitine, which

are precursors to TMAO. However, there were significant differences found with TMAO and those who consumed pork food groups to include ham, and porkchops compared to those who did not consume pork and food groups (mean difference -2.90 ± 0.98, p=0.007; Figure 3.3). Lastly, TMAO was correlated with age (r= 0.48, p=0.011).

Overall, men had a higher LVEF and were older in the sample. Sex differences for this sample were noted descriptively. There were no mean differences between men and women for both TMAO and DII. Women had slightly higher mean values of TMAO than did men, and the highest values of TNF-α (Table 3.3). Women had higher overall kilocalorie (kcal) intake (1408.11 kcal) than men (1105.89 kcal, p=.337). However, women showed DII scores that reflected more anti-inflammatory potential of their dietary intake than did men with a (total DII score -0.43 vs-0.23), indicating men consume a more inflammatory diet (Shivappa et al., 2014). Table 3.4 shows the dietary patterns for men and women to include both nutrient intake with selected food groups. Men had higher intake in the following food categories: cholesterol, choline, vegetables, proteins, alcohol, legumes, poultry, red meats, eggs, and phosphatidylcholine. Women were found to have higher intake of saturated fat, sodium, dairy, sugar, and fruit.

Women had a higher level of TNF-α as compared with men (1.76 vs 1.44 pg/ml, p=0.176). Individual lifestyle factors of BMI, alcohol intake, physical activity, and smoking habits were assessed separately with DII, TNF-α, and TMAO. There were no significant correlations with DII and obesity nor alcohol intake. A t-test for DII and BMI revealed that those with a BMI in the range of obesity (BMI ≥ 30) were found to have a negative DII score (mean score -1.20) while those who did not have obesity had a mean DII score of 1.36 (mean difference 2.57±1.32, p=.064). TNF-α was lower among participants with BMI <30 kg/m^2 as compared to those with BMI >30 kg/m^2 (mean difference -.51 ± 0.21, p=0.020; Figure 3.4).

Discussion

In this study, TNF-α was positively correlated with TMAO. There was no correlation of TMAO w with betaine, choline, or omega-3 acids. These findings were unexpected as choline is a precursor to TMAO. Omega-3-fatty acids are usually in fish products, which contain choline as well (Wiedeman et al., 2018). Betaine is another byproduct of choline and therefore linked to the metabolite TMAO (Trøseid et al., 2015). These findings might be related to the temporal relationship between measures of TMAO and the food intake questionnaire. TMAO was measured from a one-time fasting blood sample at baseline, while the FFQ calculated food components from the prior month's self-report food intake. The negative correlation between dietary choline and total DII score was an expected finding since choline is an essential nutrient and not considered to be an inflammatory component of the diet (Tang et al., 2019; Wiedeman et al., 2018). The lifestyle factors were a measure of the number of risky behaviors that might contribute to an individual's measures for inflammation either by diet (DII) or related to his or her physiological condition (TNF-α), or in relation to the types of foods they consume that may produce TMAO (Aggarwal et al., 2018). These factors assessed individually with the key variables were not found to have significant relationships except a trend in difference with DII by BMI groups between those with obesity and those without it.

Notably, there were foods considered to be non-inflammatory, such as legumes, which were negatively related to the DII score. However, there are also food groups that were inversely correlated with DII scores that would be considered inflammatory, such as beef and poultry (Christ et al., 2019). Participants in this sample were potentially consuming more anti-inflammatory foods which includes choline, and this may have counteracted the effects of the inflammatory foods consumed, producing negative DII scores, especially since the overall sample DII was negative. In a larger sample, one may expect the DII and the TMAO score to be positively correlated as the more inflammatory a person's diet, the greater the TMAO intake as documented through recent studies (Aggarwal et al., 2018), (Christ et al., 2019).

Many researchers have studied the effects of diet on different chronic conditions; especially those with an inflammatory link (Hess et al., 2021). Dietary intake, obesity, alcohol intake, and smoking have all been linked to inflammatory mechanisms and therefore warrant further attention to better manage the detriments of HF (Hess et al., 2021), (Aggarwal et al., 2018). Choline was found to be negatively correlated with DII, and therefore one needs to consider that the nutrient itself is not inflammatory and the increase of the DII may be related to the quantity of choline consumed and the type of food source (Wiedeman et al., 2018). The same would be true for TMAO; further research is needed to better understand the link between different foods with high quantities of choline and carnitine and how they affect TMAO levels (Tang et al., 2019). The fact that data from this study point to associations related to higher pork leading to higher TMAO concentrations in the blood as well as higher intake of certain nutrients (choline) leading to a lower DII score, illustrate how the diet can indeed influence mechanisms related to inflammation and could therefore serve as a targeted therapy for care in the HF population.

The differences between men and women regarding dietary intake are apparent. The DII of women is indicative of their different dietary patterns than men. Contrastingly, women had the higher measures of both TNF-α and TMAO. This could be due to the higher number of women who participated in the study as well as their higher intake of betaine and foods with saturated fat. Also, the food energy for men and women may differ and potentially influence their TMAO levels since this is a diet-linked metabolite (Tang et al., 2019). Although women appeared to have consumed more saturated fat, dairy, and carbohydrates than men, they also report consuming more whole grains, foods containing betaine, and fruit, according to the data. The women appeared to consume more anti-inflammatory foods which may be an explanation of their lower DII score in comparison with men. Even though TMAO was not significantly linked in this study with a few of its precursors and notable food sources (poultry, betaine, choline), the finding with pork intake offers some evidence of guidance for the HF population about the intake of red meat and its tendency for negative health outcomes for more reasons than just the way it is prepared or its saturated fat quantity (Kruger et al., 2017). Even in healthy populations, TMAO quantities

in the blood and urine were altered upon intake of certain foods containing choline and betaine; considering this, HF populations may need to be further counseled in food intake related to portion control needs (Kruger et al., 2017), (Aggarwal et al., 2018). Vegetables are an essential food group for all human populations so the portion control needs would be focused on the modification of meats, animal fats, eggs, pork, and similar foods groups that contain elements involved with production of TMAO (Tang et al., 2019).

The positive correlational trend between TNF-α and TMAO assert the findings of the overall aim of this study, which is that varying sources of inflammation, whether by the intake of certain foods or by the retention of gut-derived metabolites like TMAO, may influence the overall condition of HF and therefore cause worse outcomes (Shirazi et al., 2017). Lifestyle choices play a role in this inflammatory pathway as well since the data suggest that DII may be associated with weight gain as noted by the BMI. Lifestyle factors that tend to increase the inflammatory processes that exist with HF are also important to consider in the progression and prognosis of the disease. (Aggarwal et al., 2018), (Serafini & Peluso, 2016).

Limitations

We explored the impact of potential covariates but were not powered to fully test for the significance of these covariates and unable to analyze the fully hypothesized statistical models. Carnitine is not a part of the FFQ analysis, which would have been helpful in comparing DII and TMAO scores as this is a precursor in addition to choline for the metabolite TMAO. The DII was not yet adjusted for energy density which could have altered the results; the methods for this computation were not yet accessible through the Block analysis. Dietary intake was assessed with a Block FFQ that recorded intake over the past month. TMAO is directly influenced by diet and a 24-hour dietary recall may be more appropriate to connect fasting TMAO levels more precisely to dietary intake. TMAO is also directly linked with the gut microbiome which was not measured in this study; thus, we were not able to precisely link dietary intake to levels of TMAO in the blood. Lastly, this was a homogenous, well-educated group

with HF dietary guideline resources, and we cannot assume they followed a typical pro-inflammatory diet for this reason. Future research should focus on more vulnerable populations who may lack proper diet diversity, guidance, food security, and access to care.

Conclusions and Future Implications

Given the current data on TNF-α and its association with TMAO as well as the differences noted between the dietary intake of men and women, new approaches to dietary counseling should be considered for the HF populations. The capacity for inflammation is considered high when TNF-α levels escalate, and elevated TNF-α levels are associated with worse outcomes in persons with HF (Shirazi et al., 2017). There is some controversy related to the intake of fish from the diet as L-carnitine is a key nutrient in this food and intake of certain fish proteins have been linked with higher TMAO levels (Tang et al., 2019). The B/AA population may have sociocultural influences that may influence how dietary and lifestyle counseling may be accepted (Dickson et al., 2013). Portion size and quantity control of certain food items such as pork, foods containing high amounts of choline, and potentially other food groups in the Western Diet need to be further explored to ameliorate the negative effects of inflammatory-associated pathological conditions in persons with HF.

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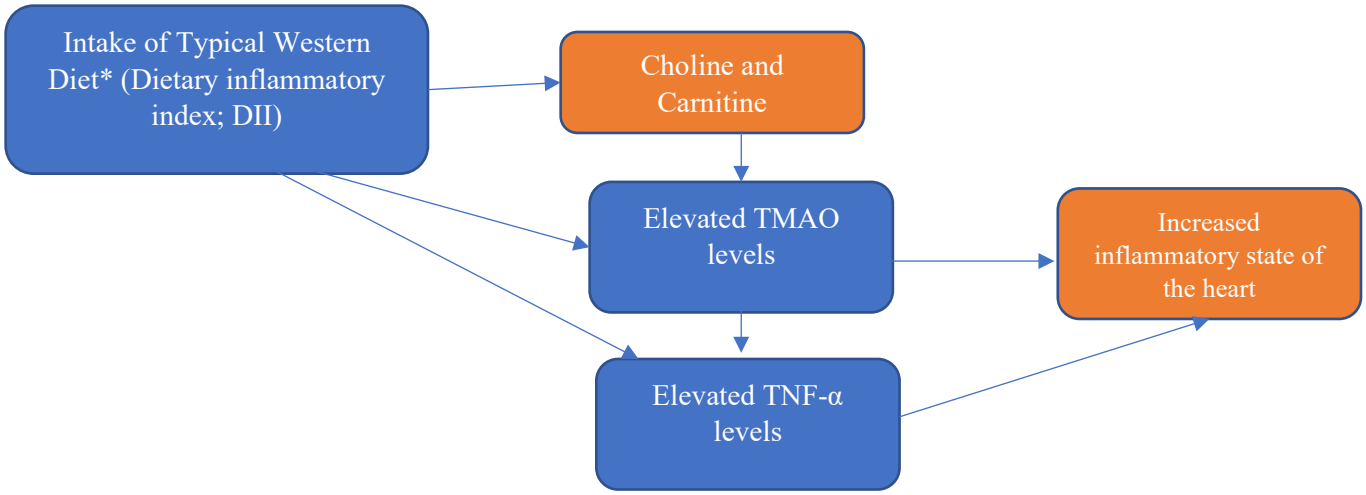
Figure 3.1. Relationship among the Western Diet, TMAO, and Inflammatory Process



*red meat, eggs, high fat foods

Figure 3.2. Positive Correlation between TMAO and TNF-α

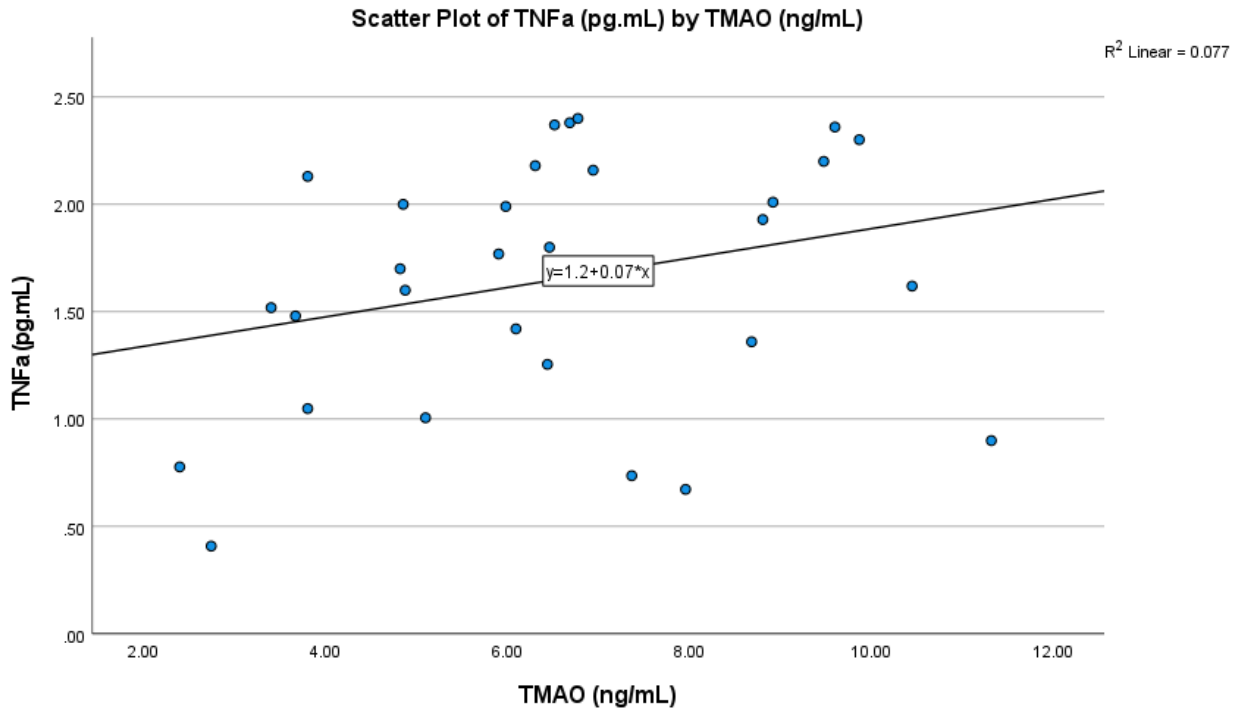
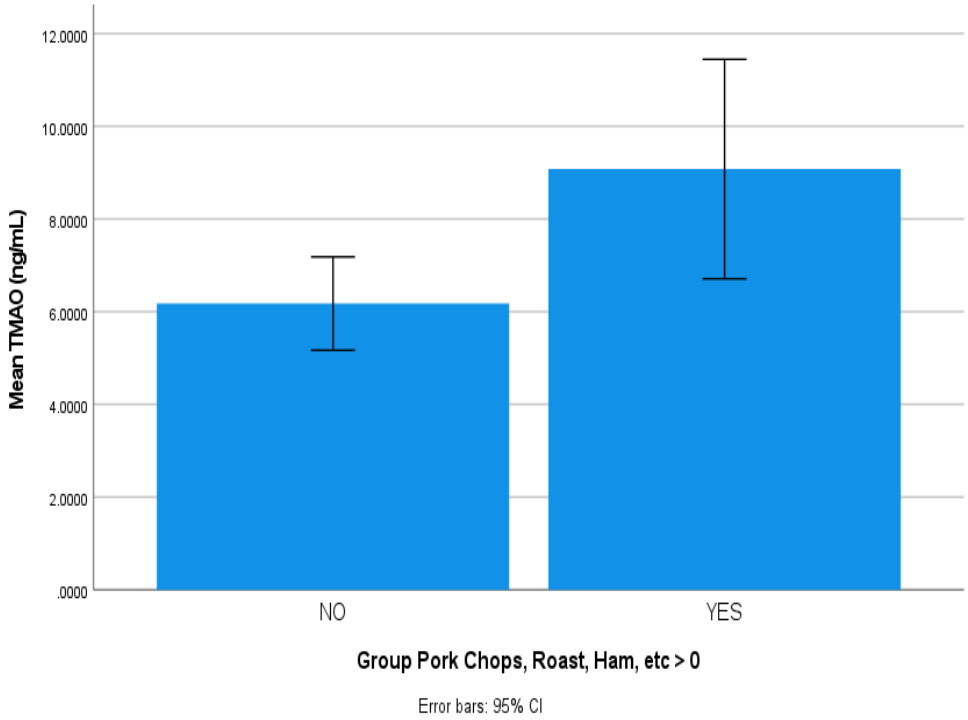
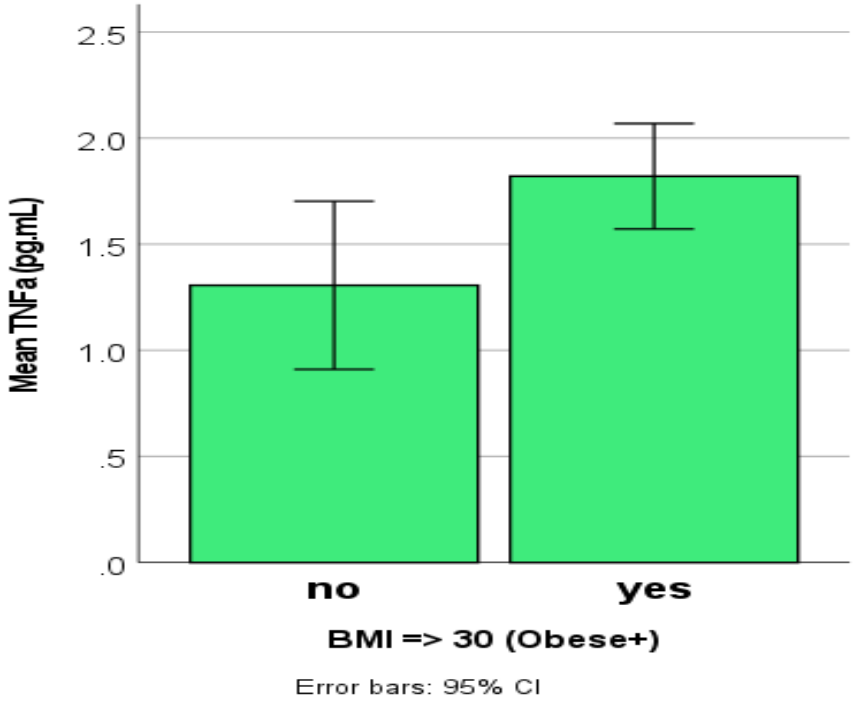


Figure 3.3. TMAO Levels by Pork Consumption



N=18 No pork consumption N=6 for Pork consumption

Figure 3.4. TNF-α and BMI Differences



N= 20 for those with obesity

N=10 for those with no obesity

Table 3.1. Baseline Characteristics of the Participant Cohort

Variable	Participants N=30
Statistics	Mean (SD)/N (%)
Age (yrs.)	55.3 (12.2)
Marital status (% married/partner)	10 (32.2%)
Education (% for some college and a degree)	25 (80.7%)
Employment (% Working now, paid, or unpaid)	14 (45.2%)
Sex	Women: 21 (67.7%)
Insurance Status (% insured)	26 (90.4%)
Race (African American/Caribbean/Black/African)	31 (100%)
Ethnicity (not Hispanic or Latino)	24 (77.4%)
Diabetes	12 (38.7%)
Chronic Lung Disease	4 (12.9%)
Chronic Kidney disease	4 (12.9%)
LVEF (%)	32.55% (13.54)
LVEF < 40 HFrEF	20 (64.5%)
LVEF ≥ 40 mildly reduced/HFpEF	11 (35.5%)
Angiotensin-Converting Enzyme Inhibitors (ACE)	4 (12.9%)
Angiotensin II receptor blockers (ARB)	7 (22.6%)
Beta Blockers	28 (90.3%)
Diuretics	31 (100%)

Key: LVEF – left ventricular ejection fraction, HFrEF- heart failure with reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction.

Table 3.2. Means and Standard Deviations of Key Study Variables

Variable	Mean (SD)
DII	-0.38 (3.24)
TMAO (ng/mL)	6.54 (2.36)
TNF-α (pg/mL)	1.65 (0.58)
Lifestyle Risk Factors (0-4)	1.90 (0.92)
CCI	2.90 (1.96)

Key: SD= standard deviation, PG- picogram, NG- nanogram, CCI- Charlson Comorbidity Index, TNF-α- tumor necrosis factor alpha, TMAO-Trimethylamine-N-Oxide., DII- dietary inflammatory index

Table 3.3. Clinical Characteristics and Key Study Variables by Sex

	Sample	N	Mean/%	Std. Deviation
LVEF % [1]	Men	9	35.28	17.43
	Women	21	32.10	11.77
TNF-α (pg/ml)	Men	9	1.44	0.61
	Women	20	1.76	0.57
TMAO (ng/ml)	Men	9	6.20	2.28
	Women	20	6.58	2.45
DII	Men	5	-0.23	4.66
	Women	19	-0.43	2.97

[1]LVEF presented as mid-point if range was recorded in the medical record.

LVEF – left ventricular ejection fraction

Table 3.4. Dietary Patterns for Men and Women

	Sex:	N	Mean	Std. Deviation
Red meat oz. eq. (Beef, veal, pork, lamb, and game meat; excludes organ meat and cured meat)	Men	5	.93	0.55
	Women	19	.61	.59
Total Vegetables cup eq	Men	5	1.50	.70
	Women	19	1.39	.75
Fruits cups eq.	Men	5	0.72	0.42
	Women	19	1.48	1.05
Fish oz eq	Men	5	.41	.25
	Women	19	.15	.15
Whole grains oz. eq.	Men	5	0.49	0.47
	Women	19	0.70	0.82
Refined grains oz. eq.	Men	5	2.04	1.20
	Women	19	2.35	1.58
Legumes cups eq.	Men	5	0.20	0.28
	Women	19	0.08	0.20
Total poultry oz. eq.	Men	5	0.84	0.51
	Women	19	0.64	0.62
Eggs oz. eq.	Men	5	0.76	0.33
	Women	19	0.40	0.35
Proteins in grams	Men	5	51.82	26.24
	Women	19	45.48	19.80
Carbohydrates in grams	Men	5	110.29	52.56
	Women	19	175.92	91.26
Fat in grams	Men	5	50.24	23.72
	Women	19	60.38	27.53
Alcohol in grams	Men	5	3.10	3.01
	Women	19	1.3	3.76
Total Dairy cup eq.	Men	5	0.61	.43
	Women	19	0.92	.61
Total Grains oz. eq.	Men	5	2.53	1.38
	Women	19	3.05	2.03
Sugar/Honey grams	Men	5	2.17	3.04
	Women	19	2.29	7.06
Total Cholesterol mg	Men	5	273.89	98.21
	Women	19	188.24	116.87
Total Saturated Fat grams	Men	5	14.89	7.32
	Women	19	18.56	9.49

Total choline mg	Men	5	265.43	104.28
	Women	19	205.94	87.50
Trans Fat total grams	Men	5	1.02	0.50
	Women	19	1.76	1.61
Glucose(dextrose) grams	Men	5	10.56	3.56
	Women	19	25.23	20.00
Choline/Phosphatidylcholine	Men	5	178.37	62.67
mg	Women	19	118.73	64.15
Betaine mg	Men	5	49.86	24.68
	Women	19	55.57	24.68
Food energy kcal	Men	5	1105.89	511.07
	Women	19	1408.11	632.90
Total sodium mg	Men	5	2077.75	1047.24
	Women	19	2221.71	1008.82
Body Mass Index (BMI) kg/m^2	Men	9	33.33	7.79
	Women	21	36.02	10.38

Key: N=count, Cup eq.= cups equivalent Oz. eq.= ounces equivalent, mg=milligrams, all units/day, kcal=kilocalories, kg/m^2= kilograms per meters squared.

Chapter 4

The Influence of the Western Diet, Trimethylamine N-Oxide, and Inflammation on Symptoms in Persons with Heart Failure

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Abstract

Introduction

Symptom burden in heart failure (HF) has been noted to have many contributing factors that stem from the physical, emotional, spiritual, and social realms of health. There are several biomarkers that have been identified as key contributors to both HF and to the depressive symptoms that persons with HF experience. The Western Diet (WD) has been found to be pro-inflammatory and is currently studied in HF populations. A more specified approach to symptom management may indicate dietary changes and the exploration of these inflammatory symptom pathways is warranted to determine more specifically how they affect symptoms and outcomes in this population.

Purpose

The purpose of this study was to examine the association of the Western Diet (WD), gut derived metabolite trimethylamine-N-oxide (TMAO), and inflammation as indicated by tumor necrosis factor (TNF-α), with physical and depressive symptoms in persons with HF.

Methods

Thirty-one self-identified Black/African American (B/AA) adults with chronic HF were surveyed on physical and psychological symptoms in HF. The Heart Failure Symptom Survey (HFSS) was used to assess physical symptoms specific to HF and the Center for Epidemiology Studies Scale (CES-D) was used to detect depressive symptoms. TNF-α and TMAO, were measured to detect systemic inflammation, and the Dietary inflammatory index (DII) was used to measure the inflammatory potential of the diet. Sociodemographic variables, such as age and sex, were measured along with social support via the Multidimensional Perceived Social Support Scale.

Results

There were six significant regression models that explained the variance of physical HF symptoms; TMAO and related covariates accounted for 37% of the change in physical symptoms ($F(7,15) = 2.843$, $p=.042$), TNF-α and related covariates were significant in predicting changes in the frequency and enjoyment of life dimensions of HF symptoms ($F(7,15) = 3.597$, $p=.018$) and ($F(7,14) =$

2.890, p=.043). Men tended to report higher physical symptom burden while women had higher depressive symptom burden, although these differences were not statistically different.

Conclusion

Several physical influences of symptoms and symptom dimensions could be further explored such as the impact of dietary intake as it is related to TMAO, TNF-α, and possible sources of inflammation in the context of sociodemographic, clinical, and social support factors. In this sample, measures of overall dietary inflammation, and biomarkers TNF-α and TMAO were not significantly associated with physical or depressive symptoms. Covariates of LVEF, age, sex, and comorbidities contributed most to the models. Small to moderate effects sizes of TMAO and TNF-α for physical HF symptoms may be used to inform a larger study with a more diverse and vulnerable population.

Introduction

Symptom burden in heart failure (HF) has many contributing factors that stem from the physical, emotional, spiritual, and social realms of health.[1] There are numerous triggers that may be related to HF symptom management, and symptom-related distress often corresponds to adverse cardiac events which lead to multiple hospital admissions and a deterioration of quality of life (QOL).[1] Inflammatory pathways contribute to both poor outcomes with HF and its associated symptoms. Several inflammatory biomarkers have been identified as key contributors to both HF and to the depressive symptoms that persons with HF experience, including TNF-α.[2] As symptom reduction is a key goal in quality treatment in HF care, [1,3] a better understanding of pathways linked to HF symptoms is needed to better understand the cause and best route to alleviate the distress.[3]

Inflammation in HF is heavily linked to the distress of symptom burden, and diet is a potentially modifiable source of inflammation in persons with HF.[3,4] Black/African American (B/AA) populations have higher mortality with HF , but little is known about the symptom patterns faced by this population.[5,6] Both emotional and physical symptoms exist within the constellation of symptoms present with HF.[7] Depression is a comorbid condition that is often associated with the total symptom burden of HF patients and has been found to contribute to mortality rates.[7] Persons with depression and HF have been found to have worse outcomes than those with no depression. As TNF-α is implicated in the pathology of both HF and depression, this inflammatory cytokine is a putative pathway leading to these worse outcomes in persons with comorbid HF and depression.[7] Inflammation may promote the progression of HF and contribute to cardiac dysfunction, and has been linked with poor prognosis.[4] Physical symptoms, specifically the sickness behavior symptom cluster that is present in HF populations, include anhedonia, fatigue, malaise, and somnolence and are thought to be provoked through the cytokine cascade.[4] Since TNF-α has been identified as a contributor to neurohormonal dysregulation in both depression and HF, it deserves more attention, and its role in symptom attribution should be explored.[7]

TNF-α has been identified in the pathophysiology of both HF and depression .[8] According to Fertekich, et. al., TNF-α levels are higher in persons with HF than in healthy populations.[8] Several studies have implicated depression as either a pre-existing factor in the development of HF or as a risk factor for negative outcomes for those with the condition.[8] TNF-α is released in response to many cardiac insults such as ischemia, viral illnesses, and toxins.[9] There are various external sources of inflammation to be explored in the symptom patterns associated with HF and its severity. Among those potential sources of inflammation are a pro-inflammatory diet and a gut derived metabolite called trimethyl-amine-N-oxide (TMAO).[10,11]

The influence of diet in HF has been a topic of discovery over the years, and several controversies exist when deciding what the best dietary modifications are for this population.[12] The Western or a pro-inflammatory diet includes the intake of high fat foods, including dairy products, sweetened and high-sugar foods, and processed grains.[13] Along with red meat, the foods comprising the Western Diet (WD) may also contribute to the buildup of certain nutrients such as choline and carnitine in the diet.[14] The metabolism of carnitine and choline can lead to the production of the metabolite TMAO.[11,14] TMAO has been linked to various outcomes of mortality and adverse cardiac events.[15] There are at least two known pathways by which TMAO may induce inflammation in the heart. These are activation of the cytokine cascade through the nuclear factor kappa B (NF-κB) signaling pathway and platelet hyperactivity leading to thrombosis. Together, these processes predispose a person to the development of atherosclerosis and other ischemic states, which may lead to the progression of cardiac disease and HF.[15]

The purpose of this study was to examine the pro-inflammatory WD, gut derived metabolite TMAO, and inflammation (as measured by TNF-α), with physical and depressive symptoms in persons with HF while controlling for related variables of age, sex, comorbidities, social support, lifestyle factors (alcohol use, body mass index (BMI), smoking, and exercise) as well as ejection fraction (EF). We hypothesized that 1) the greater the pro-inflammatory diet the higher physical and depressive symptoms,

2) the greater the TMAO level the higher the physical and depressive symptom burden, and 3) the greater the TNF-α, the higher the HF physical and depressive symptoms. The concepts of this study are aligned with the Theory of Unpleasant Symptoms which states symptoms are experienced in multiple dimensions and are influenced by three factors: situational, physiological, and psychological aspects of care.[16]

Methods

Research Design

This cross sectional, observational study was designed to address correlational aspects of the WD (typically pro-inflammatory), TMAO, TNF-α, and symptom burden in self-identified Black adults of African, African American, and Afro-Caribbean heritage (B/AA) with HF. Data collection took place between April 2021 and April 2022 and involved a hybrid data collection schema due to the Covid-19 Pandemic as described in its parent study by Butts et al.[17] Thirty-one participants were enrolled in this study from the Cardiology Clinics at Emory University Hospitals. Inclusion criteria were self-identified Black or African American adults, 30-80 years of age, diagnosed with chronic HF as defined by provider diagnosis, receiving optimal medical management, which included angiotensin converting enzyme inhibitors, angiotensin II receptor blocking agents, beta blocking agents, mineralocorticoid receptor antagonists, and diuretics, able to read, write, and understand English. Exclusion criteria were the presence of any of the following: severe chronic kidney disease with a glomerular filtration rate (GFR) of <30 ml/min/1.73m^2, in hospice care, diagnosed with an uncontrolled mental condition (i.e., schizophrenia, bipolar disorder, and major depression) as noted in medical records, receiving total parental nutrition or nutrition by a gastric tube, and uncontrolled severe hypertension (systolic >200 mmHg or diastolic >100 mmHg at baseline). This study was performed under research protocols approved by the institutional review board of Emory University.[17] Each subject was informed of study protocols and the potential risks and benefits of participation. All participants provided written consent before participation.

Measurements

Sociodemographic and Clinical Data

Sociodemographic and clinical variables included age, sex, education, insurance status, marital status, medical history, medications, and left ventricular ejection fraction (LVEF). They were obtained from medical records and a self-report questionnaire. Co-morbidities were analyzed using the Charlson comorbidity index (CCI), which quantifies the risk of death from co-morbid conditions.[19] Height was collected by self-report. Weight was measured in kilograms using a calibrated scale. Body mass index (BMI) was calculated by the formula: BMI = (weight in kg)/(height in cm)$^{2.}$ Participants with LVEF < 40% were categorized as HF with reduced ejection fraction, and those with LVEF >40% were categorized as HF with mildly reduced and preserved ejection fraction.

Questionnaires

Dietary intake over the past month was assessed using the 2014 Food Frequency Questionnaire (FFQ), a 12-category survey that reports on the frequency and quantity of foods consumed over the past month. Both standard analyses and dietary inflammatory index (DII) score were performed.[20,21] The DII estimates the inflammatory potential of the diet. DII scores <0 were anti-inflammatory, and scores greater than zero were considered pro-inflammatory. DII score was used in concurrence with the FFQ to calculate scores which show the level of inflammation as noted by inflammatory cytokines like TNF-α.[21] HF symptoms were measured with the HF Symptom Survey (HFSS), a 14-item questionnaire examining the frequency, severity, and interference of HF symptoms in daily life and with physical activity.[22] This survey measured symptoms across 4 dimensions and the mean totals were averaged for a total score. Perceived social support was assessed with the Multidimensional Scale of Perceived Social Support (MSPSS), which examined participants' social support system.[23] The Center for Epidemiological Studies scale (CES-D) was used to assess depressive symptoms and mood.[24] All surveys were made available via an electronic link that was sent to participants via email to be completed on the day of the virtual visit.

Forms were reviewed for completeness upon receipt and participants were contacted for resolution of missing data, if any. A combined lifestyle factor score included smoking, alcohol intake, exercise frequency, and BMI.

Lab Procedures and Data Analysis

Dried blood spots (DBS) were collected in the morning after an overnight fast using 30 μL Mitra® micro-sampler devices, as previously described.[17] Samples were placed in a -80°C freezer until analyses. TMAO (BioHippo) and TNF-α (Olink®) levels were analyzed using ELISA per manufacturer's directions. Duplicate analyses for samples were obtained to ensure assay fidelity.

Data analyses were performed with SPSS 27 software [25]; preliminary analyses examined variable distributions for normality, skewness, descriptive data, and outliers to see if assumptions for statistical analyses were met. Correlations and linear regressions examined the significance of the relationships with all variables and the potential covariates (age, sex, comorbidities, lifestyle factor score, social support, LVEF). The key research aim was analyzed with steps involving correlations and multiple linear regression models to examine the dietary inflammatory index (DII), TNF-α with TMAO, and the relationships between physical and depressive symptoms. For a sample size of 30 with a linear regression model testing up to1 predictor at a time and controlling for up to 6 covariates at 80% power and 5% level of significance, we were powered to detect a moderate-to-large effect size f2=0.29.

Results

A total of 31 B/AA participants were enrolled in this study, with 24 participants completing all study components (questionnaires, laboratory samples, and food survey). Participants were 34–80 years of age and 67.7% were female (Table 4.1). The mean LVEF was 32.6%. Age was positively correlated with LVEF (r=0.49, p=0.010) and CCI weighted score (r=0.48, p=0.011). Correlations were completed with TMAO, DII scores, and TNF-α along with related covariates such as age, sex, social support, LVEF, lifestyle factors, and the CCI weighted score. TMAO was positively correlated with age (r=0.40, p=0.030)

and CCI score (r=0.49, p=0.009). Social support was found to be positively correlated with the CCI score (r=0.36, p=0.050). The mean score for HF symptom severity and LVEF were found to be negatively correlated (r=-0.37, p=0.040). The mean score for HF symptoms interfering with enjoyment of life were negatively correlated with age (r=-0.42, p=0.025), and the mean score for HF symptoms interfering with enjoyment of life was inversely correlated with LVEF (r=-0.54, p=0.005).

After adjusting for the six aforementioned covariates, there was a significant association of TNF-α with physical HF symptoms that interfere with the enjoyment of life (F(7,14)=2.89, p=.043; Table 4.3). The following predictor variables explained the variation of physical HF symptoms as measured by the mean HFSS score: F(7,15)= 2.843, p=.042: sex, LVEF, social support, lifestyle risk factors (LIS) , TMAO, age, and CCI (Table 4.4). An adjusted model demonstrated a significant association of TNF-α with the frequency of HF symptoms (F(7, 15)=3.597, p=.018). There was also a significant result for an adjusted model involving the 6 covariates and TNF-α (F(7,15)=3.008, p=.035 with the mean score for HF symptoms and TMAO plus 6 covariates on HFSS/Frequency F(7, 15)=3.663, p=.017. Lastly, TMAO and related covariates were found to impact HF symptoms that interfere with enjoyment of life F(7,14)=2.812, p=.047. Tables 4.5-4.8 display these data. Table 4.10 displays the most prevalent symptoms in this sample.

An adjusted and unadjusted model was executed to examine the influence of 6 aforementioned covariates on the outcome variable CES-D or depressive symptoms in this sample of HF patients. While the regression model was not found to be significant, there were some significant correlations: social support was found to be positively correlated with co-morbidities (r=0.36, p=.050). There was a possible trend noted for CES-D which was inversely correlated with age (r=-0.34, p=.064). In comparing the mean symptom scores for both physical and emotional symptoms of HF between men and women, men were found to have higher physical symptom burden while women had a greater mean score for depressive symptoms (Table 4.9). Lifestyle factors were individually assessed with both physical and emotional symptoms links with HF. For participants with a BMI $\geq$ 30 kg/m^2, TNF-α was found to be

positively correlated with BMI. There were no other significant correlations among TMAO, DII, or TNF-α and the lifestyle factors of alcohol intake, BMI, physical activity, and smoking.

Discussion

In this study of B/AA adults with HF, we observed a significant impact on the average score for physical HF symptoms as influenced by TMAO and related covariates. Although TMAO was not significant in the model, the effect size of .122 warrants further exploration in a larger sample. We found significant results for the impact of TNF-α and related covariates on physical HF symptoms, a significant model for the effects of TNF-α and covariates on the frequency of HF symptoms, and that TNF-α and covariates had a significant influence on HF symptoms that interfere with the enjoyment of life. Although TNF-α was not significant in these models, the effect sizes of -.59, -.45, and -.75, respectively, suggest more work in a larger study is needed. The TMAO and age variables were positively correlated; this could be due to the increasing disease severity that may happen over time; since TMAO may worsen with HF severity,[26] age could be a factor with elevated levels of TMAO in the blood.[27] Several predictors in the regression model contributed to the impact of symptom burden: sex, LVEF, social support, age, and CCI.

Although it was expected that a lower LVEF would result in a higher burden of physical HF symptoms, other contributors such as increasing age and a higher CCI score were observed. TMAO was positively correlated with CCI; this suggests that the greater the number and severity of the comorbidities, the greater the association with high concentrations of TMAO. According to recent literature, high plasma levels of TMAO have been linked with atherosclerosis, mortality with cardiorenal disorders, and type 2 diabetes.[28] The fact that TMAO levels were found to increase with both age and with the number of weighted comorbid conditions in a sample of HF patients suggests the need to better understand the role of TMAO metabolism in the context of the microbiota, specific precursors with nutrient intake, as well as health status of populations which may affect both metabolism and excretion of TMAO.[28] This would be especially important to note with renal disease as TMAO is often escalated in those with renal insufficiency.[10] Although there were no direct correlations between HF symptoms and TMAO, the higher

quantities of TMAO may have a negative impact on HF symptoms, especially in the context of a lower LVEF and increasing age.[29]

The presence of chronic diseases coexisting with HF, such as depression, should be further considered as positive predictors of symptoms in this condition. The data from this study suggest that social support is also positively correlated with comorbidities which is an unexpected finding but may reflect greater social support provided to those who have a greater number of chronic illnesses. Lack of social support is reported to be a risk factor for the development of depression in HF in current literature.[30] However in this study, no relationship was found.

Age was negatively associated with HF symptoms interfering with enjoyment of life. Therefore, age may be considered when managing the symptom experience of individuals with HF as it may influence their quality of life. Coping abilities need further exploration in young adult populations, and maladaptive coping may lead to unhealthy lifestyle choices as noted in current literature where HF prevalence is rapidly changing due to modifiable risky life choices.[31,32] Symptom burden experience may be related to the amount of social support a person receives and a younger age bracket according to these findings. With the existence of comorbid conditions, like obesity and low socialization resulting from depression in HF patients, symptoms can be especially burdensome and hinder different areas of life.[33] Current research studies give insight for the holistic approach needed to attend to symptom burden in HF care.

Findings related to the physical symptom burden of HF and TNF-α were mostly expected; there was a significant link between the physical symptoms of HF and TNF- α, with relevant covariates such as age, sex, and LVEF driving the model. Despite the fact that DII was not linked directly to HF symptoms, there appears to be a clear pathway between HF symptoms as linked by TNF-α.[4] Although TNF-α was not a significant predictor in the model, the moderate effect size as part of a significant model within this small sample size suggests TNF-α may play a role in HF symptom burden. However, this does not mean diet is to be discounted with the HF population; scientific literature reports evidence that inflammatory

food patterns may be directly contributory to the condition of HF and associated symptoms with proper dietary modification needs to be solidified for better outcomes.[12,34] Given the inflammatory nature of TMAO,[31] compounded with the fact that depression is related to increased TNF- α levels in the blood,[8] dietary factors related to inflammation must be considered to improve the overall care regimen of HF patients. Symptoms continue to be a key target of care in HF, and a more precise approach to noting the cause and influence of both emotional and physical symptoms of HF will assist health care teams with effective interventions for men and women in this population.[3,35]

Some differences between men and women were found in the means and standard deviations of symptom scores, but these were not statistically significant. Based on prior studies, we expected to see differences by sex. Women tended to experience greater depressive symptoms, and men reported greater physical symptoms.[36] Current literature affirms this but also notes women may experience greater obesity, higher blood pressure, and heart rate as well. [36] In assessing symptoms in this population; greater attention should be given to the triggers and correlates to symptoms; especially emotional triggers in women.[36] The Theory of Unpleasant Symptoms dictates how multiple influential physiological, psychological, and social factors interact with symptom burden in a given population. HF patients often experience concurrent symptoms, and therefore preceding factors of these symptoms should be explored. Biological sex should be considered in the assessment of symptoms in HF as well as the other factors aforementioned as a part of a complete nursing care plan to achieve expected outcomes.[16]

Limitations

One limitation of this study was the small sample size. With a smaller effect size and sample, differences and correlations may have been affected, and therefore results are limited to details provided by this dataset. Furthermore, there were fewer men than women in this analysis which may not give a full picture of the symptom presentation. This study enrolled participants from an academic medical center, and study participants were well-educated with good access to health insurance overall. Thus, these findings are not generalizable to the HF population. Findings may vary in a different sample type and

socially disparate outcomes would be more evident which is important to note with this kind of research especially as it relates to food access and dietary education. Additionally, the gut microbiome was not analyzed for this study, and this may have influenced the TMAO levels along with dietary variables. Also, the symptoms were collected at one time point and the DII is from a one-month food frequency questionnaire, which may have influenced the ability to detect a relationship with TMAO. Lastly, this study was conducted during the time of a pandemic which could have impacted symptom reporting and other lifestyle behaviors.

Conclusion and Future Implications for Study

The findings of this study suggest that a comprehensive symptom assessment for HF patients is warranted. Greater analysis of the sickness behavior symptoms of malaise, fatigue, loss of appetite, and anhedonia is warranted as this symptom cluster is specific to both depression and HF. Such a study could determine the relevance of this cluster in HF care.[4] Several dimensions of symptoms must be explored such as the physical influence of dietary intake as it is related to TMAO,[31] comorbidities, social, and lifestyle factors such as BMI, exercise habits, and alcohol intake, and possible sources of inflammation, especially as contributed by one's diet.[31,37] Physical, situational, and emotional factors as linked to the social determinants of health need to be further explored in the HF population, especially among African Americans who have been found to experience less than desirable outcomes with this disease.[5]

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Table 4.1. Sociodemographic and Clinical Variables

Variable	Participants N=31
Statistics	Mean (SD)/N (%)
Age and range (yrs.)	55.3 (12.2)
Marital status (% married/partner)	10 (32.2%)
Education (% for some college and a degree)	25 (80.7%)
Employment (% Working now, paid, or unpaid)	14 (45.2%)
Sex	Men: 10 (32.2%) Women: 21 (67.7%)
Insurance Status (% insured)	26 (90.4%)
Race (African American/Caribbean/Black/African)	31 (100%)
Ethnicity (not Hispanic or Latino)	24 (77.4%)
Diabetes	12 (38.7%)
Chronic Lung Disease	4 (12.9%)
Kidney disease	4 (12.9%)
LVEF (%)	32.55% (13.54)
LVEF < 40 HFrEF	20 (64.5%)
LVEF ≥ 40 Mid-range/HFpEF	11 (35.5%)
Angiotensin-Converting Enzyme Inhibitors (ACE)	4 (12.9%)
Angiotensin II receptor blockers (ARB)	7 (22.6%)
Beta Blockers	28 (90.3%)
Diuretics	31 (100%)

Key: HFrEF- heart failure with reduced ejection fraction, HFpEF-heart failure with preserved ejection fraction

Table 4.2. Study Variables

Variable	Mean (SD)
HFSS Total	0.92 (1.44)
CESD	10.76 (12.32)
DII	-0.38 (3.24)
TMAO (ng/mL)	6.54 (2.36)
TNF-a (pg/mL)	1.65 (0.58)
Lifestyle Risk Factors (0-4)	1.90 (0.92)
LVEF	32.55 (13.54)
CCI	2.90 (1.96)
MSPSS	5.81 (1.89)

Key: SD= standard deviation, PG- picogram, NG- nanogram, MSPSS-Multidimensional Scale of Perceived Social Support, CCI- Charlson Comorbidity Index, TNF-α- tumor necrosis factor alpha, TMAO-Trimethylamine-N-Oxide., DII- dietary inflammatory index, HFSS- heart failure symptom survey, CESD- Center for Epidemiology Studies Depression Scale

Table 4.3. Regression Analyses for TNF-α and Heart Failure Symptoms-Interference with Enjoyment of Life

	Model (unadjusted): HFSS Intf w/EL with TNF-α						Model (adjusted): HFSS Intf w/EL with TNF-α Adjusted for covariates					
	B	SE_B	β	p-value	95% CI LB	95% CI UB	B	SE_B	β	p-value	95% CI LB	95% CI UB
(Constant)	1.278	1.082		.251	-.979	3.535	10.954	2.810		.002	4.927	16.982
TNF-α	-.234	.625	-.083	.712	-1.537	1.070	-.448	.562	-.160	.439	-1.653	.758
lifestyle							.138	.340	.077	.690	-.591	.868
Age							-.081	.032	-.607	.023	-.149	-.013
Sex							-1.579	.802	-.415	.069	-3.299	.141
LVEF							-.048	.023	-.419	.059	-.098	.002
CCI							.345	.173	.450	.066	-.025	.715
MSPSS							-.282	.167	-.337	.114	-.641	.077
Model Fit	Change in R2 = 0.007 (p=.712) R2 (unadjusted) = 0.007 Adjusted R2 = -0.043 Model F(1,20) = 0.140, p=.712						Change in R2 = 0.584 (p=.030) R2 (unadjusted) = 0.591 Adjusted R2 = 0.387 Model F(7,14) = 2.890, p=.043					

Key: TMAO- trimethylamine-N-oxide, MSPSS- multidimensional scale of perceived social support, LVEF-left ventricular ejection fraction.

Table 4.4. Regression Analysis for Total Physical Heart Failure Symptoms and TMAO

	Model (unadjusted): HFSS Total with TMAO						Model (adjusted): HFSS Total with TMAO Adjusted for covariates					
	B	SE_B	β	p-value	95% CI LB	95% CI UB	B	SE_B	β	p-value	95% CI LB	95% CI UB
(Constant)	.290	.949		.763	-1.685	2.264	9.259	2.635		.003	3.641	14.876
TMAO	.118	.137	.184	.401	-.168	.404	.122	.129	.190	.359	-.152	.396
lifestyle							-.091	.302	-.055	.768	-.734	.553
Age							-.069	.031	-.550	.040	-.134	-.004
Sex							-1.552	.666	-.458	.034	-2.972	-.131
LVEF							-.047	.021	-.435	.045	-.092	-.001
CCI							.413	.171	.570	.029	.049	.777
MSPSS							-.321	.156	-.405	.058	-.655	.012
Model Fit	Change in R2 = 0.034 (p=.401) R2 (unadjusted) = 0.034 Adjusted R2 = -0.012 Model F(1,21) = 0.735, p=.401						Change in R2 = 0.536 (p=.034) R2 (unadjusted) = 0.570 Adjusted R2 = 0.370 Model F(7,15) = 2.843, p=.042					

Key: TMAO- trimethylamine-N-oxide, MSPSS- multidimensional scale of perceived social support, LVEF-left ventricular ejection fraction.

Table 4.5. The Influence of TNF-α and Related Covariates on HF Symptom Frequency

	Model (unadjusted): HFSS Frequency (adj) with TNF-α						Model (adjusted): HFSS Frequency (adj) with TNF-α Adjusted for covariates					
	B	SE_B	β	p-value	95% CI LB	95% CI UB	B	SE_B	β	p-value	95% CI LB	95% CI UB
(Constant)	2.028	1.052		.067	-.159	4.215	10.169	2.610		.001	4.606	15.732
TNF-α	-.451	.600	-.162	.460	-1.698	.796	-.749	.502	-.269	.157	-1.820	.322
lifestyle							-.028	.317	-.016	.931	-.704	.648
Age							-.053	.030	-.396	.095	-.116	.010
Sex							-1.526	.691	-.424	.043	-2.999	-.052
LVEF							-.058	.021	-.507	.016	-.103	-.013
CCI							.603	.161	.781	.002	.259	.946
MSPSS							-.305	.156	-.361	.069	-.637	.027
Model Fit	Change in R2 = 0.026 (p=.460) R2 (unadjusted) = 0.026 Adjusted R2 = -0.020 Model F(1,21) = 0.567, p=.460						Change in R2 = 0.600 (p=.013) R2 (unadjusted) = 0.627 Adjusted R2 = 0.452 Model F(7,15) = 3.597, p=.018					

Key: TMAO- trimethylamine-N-oxide, MSPSS- multidimensional scale of perceived social support, LVEF-left ventricular ejection fraction.

Table 4.6. The Influence of TNF-α and Related Covariates on the Total Mean of HF Symptoms

	Model (unadjusted): HFSS Total (adj) with TNF-α						Model (adjusted): HFSS Total (adj) with TNF-α Adjusted for covariates					
	B	SE_B	β	p-value	95% CI LB	95% CI UB	B	SE_B	β	p-value	95% CI LB	95% CI UB
(Constant)	1.539	.996		.137	-.532	3.609	9.922	2.590		.002	4.401	15.443
TNF-α	-.290	.568	-.111	.614	-1.471	.890	-.594	.499	-.227	.252	-1.657	.469
lifestyle							.060	.315	.037	.850	-.610	.731
Age							-.064	.029	-.511	.046	-.127	-.001
Sex							-1.296	.686	-.383	.079	-2.758	.167
LVEF							-.053	.021	-.491	.024	-.098	-.008
CCI							.492	.160	.679	.008	.151	.833
MSPSS							-.307	.155	-.386	.066	-.636	.023
Model Fit	Change in R2 = 0.012 (p=.614) R2 (unadjusted) = 0.012 Adjusted R2 = -0.035 Model F(1,21) = 0.262, p=.614						Change in R2 = 0.572 (p=.024) R2 (unadjusted) = 0.584 Adjusted R2 = 0.390 Model F(7,15) = 3.008, p=.035					

Key: TMAO- trimethylamine-N-oxide, MSPSS- multidimensional scale of perceived social support, LVEF-left ventricular ejection fraction.

Table 4.7. The Influence of TMAO on HF Symptoms Frequency

	Model (unadjusted): HFSS Freq (adj) with TMAO						Model (adjusted): HFSS Freq (adj) with TMAO Adjusted for covariates					
	B	SE_B	β	p-value	95% CI LB	95% CI UB	B	SE_B	β	p-value	95% CI LB	95% CI UB
(Constant)	-.238	.965		.808	-2.246	1.770	9.222	2.598		.003	3.685	14.759
TMAO	.233	.140	.342	.110	-.057	.524	.197	.127	.290	.141	-.073	.468
lifestyle							-.226	.297	-.129	.458	-.861	.408
Age							-.061	.030	-.459	.061	-.125	.003
Sex							-1.854	.657	-.515	.013	-3.254	-.453
LVEF							-.049	.021	-.432	.033	-.094	-.005
CCI							.484	.168	.627	.012	.125	.842
MSPSS							-.323	.154	-.382	.054	-.651	.006
Model Fit	Change in R2 = 0.117 (p=.110) R2 (unadjusted) = 0.117 Adjusted R2 = 0.075 Model F(1,21) = 2.785, p=.110						Change in R2 = 0.514 (p=.023) R2 (unadjusted) = 0.631 Adjusted R2 = 0.459 Model F(7,15) = 3.663, p=.017					

Key: TMAO- trimethylamine-N-oxide, MSPSS- multidimensional scale of perceived social support, LVEF-left ventricular ejection fraction.

Table 4.8. TMAO, Covariates, and HF Symptoms that Interfere with Enjoyment of Life

	Model (unadjusted): HFSS Intf w/EL with TMAO						Model (adjusted): HFSS Intf w/EL with TMAO Adjusted for covariates					
	B	SE_B	β	p-value	95% CI LB	95% CI UB	B	SE_B	β	p-value	95% CI LB	95% CI UB
(Constant)	.784	1.043		.461	-1.392	2.960	10.531	2.854		.002	4.409	16.652
TMAO	.017	.150	.026	.910	-.296	.331	.088	.139	.130	.537	-.210	.385
lifestyle							.035	.329	.020	.916	-.671	.741
Age							-.085	.033	-.636	.021	-.155	-.015
Sex							-1.809	.750	-.475	.030	-3.417	-.201
LVEF							-.043	.023	-.374	.085	-.093	.007
CCI							.289	.184	.377	.138	-.105	.684
MSPSS							-.295	.168	-.353	.100	-.654	.065
Model Fit	Change in R2 = 0.001 (p=.910) R2 (unadjusted) = 0.001 Adjusted R2 = -0.049 Model F(1,20) = 0.013, p=.910						Change in R2 = 0.584 (p=.032) R2 (unadjusted) = 0.584 Adjusted R2 = 0.377 Model F(7,14) = 2.812, p=.047					

Key: TMAO- trimethylamine-N-oxide, MSPSS- multidimensional scale of perceived social support, LVEF-left ventricular ejection fraction.

Table 4.9. Differences Between Men and Women with Symptom Scores

	Sex:	N	Mean	Standard Deviation	P-values
Physical Heart Failure Symptoms (HFSS)	Men	8	1.24	1.99	p=.461
	Women	19	0.78	1.18	
Depressive Symptoms (CES-D)	Men	8	10.63	9.61	p=.971
	Women	17	10.82	13.69	

Table 4.10. Top Symptoms for HF and Depressive Symptoms

Top HF and Depressive Symptoms	
1. Fatigue/Tiredness 64.0% 2. Shortness of breath at rest 44.4% 3. Shortness of breath with activity 42.3% 4. Dizziness 37.0% 5. Bloating 34.6%	1. Did not feel hopeful for the future 46.2% 2. Restless Sleep 42.3% 3. Did not feel as good as others 40.0% 4. Felt everything was an effort 38.5% 5. Felt Lonely 38.5%

Chapter 5

Discussion and Synthesis

The **purpose** of this dissertation study was to explore the impact of the Western diet on inflammation as a pathway for symptom control in Black/African American adults (B/AAs) living with heart failure (HF) (n=31). This study examined relationships among physical and psychological symptoms, pro-inflammatory dietary patterns (dietary inflammatory index, DII), inflammation (TNF-α), and the metabolite trimethylamine-N-oxide (TMAO) while controlling for covariates of age, comorbidities, sex, lifestyle factors (LIS [alcohol, smoking, obesity, physical activity]), social support (Multidimensional Scale of Perceived Social Support, MPSSS), and left ventricular ejection fraction (LVEF). The Heart Failure Symptom Survey (HFSS) and the Center for Epidemiological Studies Depression Scale (CES-D) were used to assess physical and depressive symptoms associated with heart failure.

This study had 2 primary aims which were: (1) to explore the relationships among pro-inflammatory diet (Diet Inflammatory Index; DII), inflammation (TNF-α), and the gut metabolite TMAO and (2) examine the pro-inflammatory diet (DII), gut derived metabolite TMAO, and inflammation (TNF-α), with physical (HFSS) and depressive (CES-D) symptoms in heart failure patients while controlling for the related covariates. This paper will discuss the findings of the study in the context of the scientific framework, examine the strengths and limitations, and present a summary of recommendations for future research and clinical practice.

Summary of the Study

For Aim 1, the hypothesis presented was that higher TNF-α levels in the blood of persons with HF would be related to an increased intake of inflammatory foods as indicated by the DII. The second hypothesis of aim 1 projected a higher TMAO level for participants that showed a higher DII. Lastly, higher TMAO levels were hypothesized to be greater in participants with higher levels of TNF-α. The findings of aim 1 showed a positive correlation between TNF-α and TMAO; the higher the TMAO, the

higher the TNF-α (r=0.28, p=.138). There were no other significant correlations found between the DII score and TMAO or TNF-α levels.

Analyses that extend beyond the scope of this aim were conducted to further understand the correlations between dietary intake, differences between men and women, lifestyle factors and key variables of DII, and TNF-α. Further in-depth exploration of food groups reported from the Food Frequency Questionnaire (FFQ) analysis used to calculate the DII were examined for linkages with TMAO since it is a metabolite of the precursors choline, phosphatidylcholine, and betaine, all of which are components of many food groups included in a pro-inflammatory diet. Differences in dietary intake were observed between men and women, and lifestyle factors were associated with certain outcomes. Findings demonstrated that dietary choline was inversely correlated with the DII score (r= -0.73, p<.001), as well as phosphatidylcholine (r=-0.43, p=.033), and a significant difference was found with TMAO and those who consumed pork food groups to include ham and porkchops compared to those who did not (-2.90 ± 0.98, p=.007) (mean ± standard error difference). In considering the different food intake levels and variables related to diet such as TMAO, women were found to have higher values of TMAO than men, and women had the highest values of TNF-α. However, women were found to have a lower DII score than men which was an interesting finding in relation to the TMAO and TNF-α levels for women.

To gain a clearer picture of what was driving the lower DII scores for women, an analysis examining differences in dietary patterns between men and women was performed. Women were found to have higher saturated fat, sodium, betaine, dairy, sugar, and fruit intake. Men were found to have higher consumption of cholesterol, choline, vegetables, proteins, alcohol, legumes, poultry, red meats, eggs, and phosphatidylcholine. Women were found to have higher overall kilocalorie (kcal) intake (1408.11 kcal) than men (1105.89 kcal). Findings from these analyses provided insight that women may have more inflammatory markers due to their higher intake of calories, sugar, saturated fat, and foods that otherwise comprise the Western (pro-inflammatory) diet.[1] However, their DII scores were lower overall, and this may be explained by their overall intake of foods that counteract the inflammatory nature of added sugars and saturated fat. This suggests that quantity of dietary intake and portion control may have an overall

effect on the diet. Some findings related to dietary intake with sex differences are congruent with results in literature reporting that women had higher intake of carbohydrates and men with higher intake of lipids.[2]

The function of metabolites like TMAO and indices like the DII may play in important role in dietary aspects of HF management.[3] A growing body of literature notes the importance of dietary management in HF and also how lifestyle factors, age, and culture share influences throughout the care regimen provided for HF patients.[4-6] The findings of this study further showed that TMAO was positively correlated with the Charlson Comorbidity Index (CCI) ($r=0.58$, $p=.002$) and with age ($r= 0.48$, $p=.011$). TMAO is an emerging metabolite of interest in HF research due to its link to poor outcomes and mortality in the HF population.[7] The fact that TMAO levels were also found to increase with age and with the number of weighted comorbid conditions in a sample of HF patients increases concern and raises awareness of the need to better understand the role of TMAO metabolism in the context of the microbiota, specific precursor nutrient intake, and age as well as health status of populations which may affect both metabolism and excretion of TMAO.[3,8] However, more studies are warranted to understand the relationship between TMAO and age. Current literature states there are changes in the gut microbiota with age; since intestinal microbiota play a role in the synthesis of TMAO, more research with TMAO in context of age and dysbiosis with the gut microbiome are needed.[3,5] Age and comorbidities must be especially noted when caring for those with HF as they may indicate the need for education towards the consumption of foods not traditional for culture and the reduction of foods that may be culturally congruent; precision therapy in this respect needs to be further explored for appropriate lifestyle changes.[5]

Analyses were performed with the individual assessment of four lifestyle factors thought to influence cardiovascular health: body mass index (BMI), alcohol intake, physical activity, and smoking.[9,10] Those with a BMI in the range of obesity (BMI ≥ 30 kg/m^2) were found to have a negative DII score (mean score -1.20), while those who did not have obesity had a mean DII score of 1.36 (2.57 ± 1.32, $p=.064$). TNF-α was higher in persons with BMI ≥ 30 kg/m2 versus those with BMI < 30

kg/m^2 (- 0.51± 0.21, p=.020). These findings highlight the importance of monitoring the inflammatory aspects of the diet versus assuming that those with a higher BMI would have a higher DII. Additionally, the DII may need further exploration as a dietary measurement tool to be sure it accounts for differences with nutrient density and BMI. This would prompt a researcher to explore foods that may be considered less inflammatory but also cause weight gain, such as different kinds of carbohydrates.[1] TNF-α was found to be higher in those with a BMI in the obesity range; which may suggest the importance of eliminating inflammatory sources of food in order to promote better weight control.[4] It is also important to consider the inflammatory profile as it may be related to the adiposity of individuals with a BMI that is within the range of obesity.[11] Another reason for this finding may be that those participants in the obese range for the BMI may have already received dietary counseling and consumed foods that counteracted inflammation. This warrants further research to determine whether other factors are contributing to the lower DII score but higher TNF-α in individuals found to be obese Overall, the Western lifestyle along with the Western diet is being highlighted in current studies; the lifestyle predisposes a person to immune system changes due to exposures to air pollution, microbial disease, and high stress levels which can promote inflammation in the body, especially with the consumption of a pro-inflammatory Western diet.[1,12] Such risk for inflammation in persons with HF may contribute to their declining health status and poor symptom control.[13]

Heart failure symptoms must be examined not just in the context of inflammation, but also in the context of depressive symptomatology as depression and HF have been found to share common inflammatory pathways, including TNF-α.[13,14] With aim 2, the Western Diet (DII) with the metabolite TMAO and TNF-α were investigated with physical and depressive symptoms in HF. The hypothesis was that increased pro-inflammatory dietary patterns, as indicated by the DII, would be related to higher physical and depressive symptoms. The greater the TMAO levels, the higher the physical/emotional symptoms in HF, and the greater the TNF-α, the greater physical HF and depressive symptoms.

Covariates that were controlled for in this aim were age, sex, comorbidities, lifestyle factors (as aforementioned), social support, and left ventricular ejection fraction (LVEF).

The findings from this aim were as follows: a significant regression model was noted for the influence of TNF-α with controlled variables on physical symptoms of HF that interfere with the enjoyment of life ($F(7,14) = 2.89$, $p=.043$). TNF-α was not a significant predictor; however, there were certain covariates that contributed mostly to the outcome of HF symptom, such as age and sex. The following predictor variables explained the variation of physical HF symptoms as measured by the HFSS for the second significant model ($F(7,15) = 2.843$, $p=.042$): sex, LVEF, social support, lifestyle risk factors (LIS), TMAO, age, and CCI scores. There were no findings related to the impact of DII on HF symptom burden. An adjusted model for the influence of TNF-α on the frequency of HF symptoms was examined with the aforementioned covariates and was found to be significant ($F(7,15) = 3.597$, $p=.018$). There was also a significant result for an adjusted model involving the 6 covariates and TNF-α ($F(7,15) = 3.008$, $p=.035$) with the mean score for HF symptoms. TMAO and the related covariates were also found to be significant in an adjusted model examining the influence of these factors on the frequency of HF symptoms ($F(7, 15) = 3.663$, $p=.017$) and symptoms that interfere with the enjoyment of life ($F(7,14) = 2.812$, $p=.047$). TNF-α and TMAO may play a role in HF symptoms in conjunction with predisposing factors related to the symptom burden, although they were not significant predictors in this sample. This was likely due to the small sample size. Factors that were most influential in the model were: LVEF ($p=.045$), age ($p=.040$), sex ($p=.034$), and the CCI scores ($p=.029$), which shows the impact of lower LVEF, younger age, male sex, and higher comorbidities on symptom burden, as congruent with literature.[13] HF patients experience a combination of issues related to symptom burden that need to be better understood so that patient-centered care with symptom management can lead to precise interventions.[15]

The assessment of and intervention for symptoms in HF should consider the physical state of a person in relation to age, the factors thought to contribute to the progression of HF, and the patient's

physiological, pathological, situational differences such as sex, LVEF, and other chronic conditions .[4] More findings from aim 2 show the correlational links between age and CCI scores (r=0.48, p=.011). LVEF was also positively correlated with age (r=0.49, p=.010). The HF symptom severity score and LVEF were found to be negatively correlated (r=-0.37, p=.040), as well as mean score for HF symptoms interfering with enjoyment of life was negatively correlated with age (r=-0.42, p=.025). The mean score for HF symptoms interfering with enjoyment of life was inversely correlated with LVEF (r=-0.54, p=.005). These data suggest that, in addition to managing physical inflammatory influences in HF, one must consider the context of a person's age, comorbidities, sex, LVEF, along with their psychosocial needs. Symptoms interfering with quality of life were directly related to age, suggesting a need to address HF symptoms across the lifespan as younger people with HF may struggle to adjust to new conditions that affect their quality of life. They would need more support with managing symptoms that interfere with daily activities.[16]

With the existence of comorbid conditions, like obesity and depression, leading to low socialization in HF patients, symptoms can be especially burdensome and hinder different areas of life.[17] The last of the findings for aim 2 were reflective of current research studies and give insight for the holistic approach needed to attend to symptom burden in HF care Social support was found to be positively correlated with co-morbidities (r=0.36, p=.050), which could reflect greater perceived support provided to those with greater number of chronic illnesses. There was a possible trend noted for the Center for Epidemiological Studies Depression scale (CES-D) which was inversely correlated with age (r=-0.34, p=.064). Men were found to have higher physical symptom burden (Heart Failure Symptom Survey score (HFSS), while women had a greater mean score for depressive symptoms (CES-D score). The symptom experience of men and women differed in this study but not with significant differences, which is similar to previous studies. Issues related to sample size and small number of men warrant further study examining differences in symptom experiences between men and women. The difference in depressive symptoms may also reflect the greater tendency for women to report psychosocial distress than

men.[18],[19] Symptom burden experience can also be related to amount of social support a person receives, and a younger age bracket as mentioned before. This information may be helpful for practice as it assists providers and nurses in understanding the individual and subjective nature of symptoms and journey of the person experiencing them.[19,20]

The Theory of Unpleasant Symptoms

This study was grounded in a theory that frames the factors influencing symptoms through physiological, psychological, and situational variables. Ultimately, the interconnected factors influencing several dimensions of the symptom experienced impact the functional and cognitive performance of the patient and potentially lead to poor quality of life and frequent rehospitalizations.[21] The Theory of Unpleasant Symptoms (TOUS) posits the multiple influences from physiological, psychological, and social factors and how they interact with symptom burden in a given population.[22] Heart failure patients often experience concurrent symptoms, and therefore preceding factors of these symptoms were explored. The TOUS provided a foundation for assessing these factors more coherently in the context of this dissertation study.

Psychological influences in this study were accounted for through the examination of social support since low socialization is common in HF patients experiencing depression and lack of a caregiver or family support system.[14,15] Social support was found to be positively correlated with CCI scores, which reflects the need for HF patients to have social support in the context of severe disease and multiple comorbidities. Situational variables in this study were defined as the individual's health status such as lifestyle factors, management of the comorbidities, preceding factors such as sociodemographic status, and other health related factors like LVEF and HF severity. Physiological variables influencing symptom burden in this study were TMAO levels, TNF-α, and dietary patterns. All of the influencing factors work together and can have either a negative or a positive influence on the experience of symptoms in the person facing HF. [22]

This study presented HF findings aligned with the TOUS in that lower LVEF influenced symptom burden distress as it interferes with the quality of life. The lower the LVEF, the higher the interference with the quality of life. The TOUS illustrates symptom burden in a multidimensional fashion characterized by frequency (timing), distress, quality, and intensity.[23] Unfolding the layers of each symptom experience and observing the triggering influence of the symptom, whether it is considering the LVEF, lack of support, age, sex of a person, or even dietary patterns, will assist health professionals in knowing the best approach to intervention.[22,23] Considering the dimensions of each symptom experience causes the professional to consider the root cause or main influence of the symptom experienced and which direction one should lead their care.[23] Another example are the predictors that were found to influence variation in the outcome of physical HF symptom frequency. The covariates in this study plus the key variable TNF-α were noted, together, to influence the frequency or occurrence of symptoms as postulated in the TOUS. The TOUS served adequately as a model for the exploration of this symptom study. This study involved a priori assumptions about symptom experiences in persons with HF and how they may be best assessed and alleviated.[23,24]

Methodology

This project was a sub-study of a larger project affiliated with the P30 Emory Symptom Science Center within the School of Nursing research core. This research was approved by the Institutional Review Board as an adjoint project of its' parent study: *Metabolomic Pathways to Fatigue, Depression, Anxiety, and Dyspnea in Black Adults with Heart Failure and Hypertension* (B. Butts, PI).[25] The parent study was originally planned as an in-person, observational study by which blood specimens would be collected via venipuncture. Due to restrictions put in place during the COVID-19 research ramp down at Emory University and Emory Healthcare, the study was transformed into a remote study involving the procedures of micro-sampling and self-collection of blood by the participants in a virtual home visit structure.[25] A hybrid design was developed in 2021 by adding an option for in-person visits; this approach was both effective and successful. It began with remote recruitment of outpatients with HF and as

restrictions were eased, the study progressed into a clinic recruitment setting where patients had the option of completing their research visit in a medical office setting with a research team member collecting samples.

Study Limitations and Strengths

Convenience sampling posed a threat to external validity as it involved self-selection in the study. Participants were interviewed using a brief questionnaire to discuss their medical history and although charts were also reviewed, this may not have been a complete picture of their medical status. This study was also performed in a stable, medically managed group predominated by participants identifying as women. More men would need to be recruited for the study to better identify differences between men and women with symptoms, dietary patterns, and other measured biological variables. The participants also tended to be well-educated and possessed health insurance; a study of this nature may need to be performed in a health setting or population that is subject to more vulnerability with their healthcare to strengthen and generalize the findings and assist health professionals in noting the variability in social determinants of health and their effects on symptom burden in the HF population. Socio-cultural influences with diet must be considered in this population. While this study successfully recruited a homogenous B/AA sample, a key factor to consider is that participants were recruited in a university-based setting that puts high value and emphasis on HF patient education and self-care management. Thus, the participants were not consuming an overall pro-inflammatory diet, and patients may have been educated against this. However, HF diet knowledge was not measured in this study which limits certainty that this is the case. The study involved a small sample size and many of findings may be more notable in a larger sample size with more power. The DII score did not include all of the precursors for TMAO, such as carnitine, as expected, and it was not adjusted for food energy. Symptom perception was also potentially influenced by an ongoing pandemic, and this would need to be considered.

The study did have several strengths to note in that it promotes nursing research with underserved populations like B/AAs and sought to explore the differences with lifestyle factors as well as attend to the

sociocultural influences of diet and symptoms in this group. Examining the individual lifestyle factors across the symptom experience with many influencing factors is very important for ongoing HF research especially for different race and ethnic groups as these lifestyle and behavioral factors may vary.[4,5] Furthermore, this study utilized the TOUS, which sets up a multidimensional approach to symptom-focused research as well as implications for clinical practice with its findings that suggest the need for greater symptom trigger assessment along with the inclusion of one's situational, physiological, and psychological context. The study also accounted for the dimensions of symptoms experienced by B/AA persons with HF and how this might contribute to symptom reporting and the development of interventions to improve the symptom. Despite the small sample size, the study did have key findings that were in line with literature and also present a foundation for continuing research in the areas of HF symptom burden control and quality of life.

Summary: Implications for Future Research and Clinical Practice

Current literature asserts that HF patients have trouble with symptom recognition, ascribing their symptoms to the right source, and distinguishing symptoms of HF from their comorbid conditions.[24] Also, multiple admissions to the hospital does not guarantee improvement of symptoms among HF patients.[24] In addition, various articles note that there is a growing need for stronger guidelines in diet therapy in the HF population as the Western diet and lifestyle influences are greatly contributing to the negative change in the prevalence and incidence of HF over a period of time.[4,26] Future research with this topic may involve the gaps aforementioned along with the sociocultural influences of diet planning and education in managing symptoms.[5] The concepts of diet diversity and diet quality need to be explored cross-culturally so that many cultures of persons experiencing HF and its symptoms can properly benefit for a change in their self-care, especially for dietary intake.[6,27] This study did not specifically measure other aspects of self-care other than diet, alcohol, physical activity, and a better assessment of self-care including medication maintenance may be important in comprehensively understanding the impact on symptoms. Research of the future related to this topic may also examine practical strategies for assisting patients with

food access, detailed and personalized diet education as well as, greater symptom trigger identification. Additionally, other inflammatory biomarkers would need to be explored in this population such as interleukin-6 and its influence on HF symptoms as well as depression.[13]A study of this nature would be best done with a multi-site set up accounting for patients with varying socioeconomic backgrounds as well as increased diversity in the sample with respect to external determinants of health. Clinical practice recommendations would involve the education of practicing registered nurses, nurse practitioners, physicians, and patients to improve self-care with the uptake of new dietary measures and more effective guidelines for precision diets and adherence to healthy lifestyle choices.[3,4]

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