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Heart failure symptom burden, dietary intake, and inflammation: An integrative review of the literature

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Abstract

Heart failure (HF) is characterized by high 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 adults (B/As) 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. 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-alpha (TNF-α), a biomarker of inflammation, and trimethylamine-N-Oxide (TMAO). 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. The literature reviewed in this study demonstrates that more work is needed to examine dietary planning, social support, and differences between men and women in the B/A 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.

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Conflicts of interest

There are no conflicts of interest.

Keywords

Depression; diet/dietary patterns; heart failure; inflammation; symptom burden; trimethylamine-N-oxide

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 adults (B/As) have higher risks for HF due to increased rates of hypertension and cardiometabolic risks compared to other adults from different racial backgrounds, have an earlier onset of HF, and have a 30%–44% higher 5-year mortality rate as compared with other race and ethnic groups.[2] Symptoms for B/As with HF are often influenced by social and behavioral factors, such as low adherence 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/As have a cultural history of eating foods with high fat and refined 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 is important to research because it examines the evidence of the relationships among HF symptoms, inflammation with oxidative stress, quality of life, self-care, diet composition and lifestyle factors, the gut derived metabolite trimethylamine-N-Oxide (TMAO), and other influencing factors such as cultural patterns and sex. Yet few interventions have addressed these variables and little evidence to guide nutritional practices to reduce symptoms in HF exist. Thus, this literature review will examine the relationships among physiologic pathways in HF and symptom burden in the context of inflammation, dietary intake, tumor necrosis factor-alpha (TNF-α), a biomarker of inflammation, and TMAO.

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] 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] TNF-α is another inflammatory biomarker found to be significantly related to emotional and physical symptoms of HF patients.[22] This review will cover topics related to each factor described as they contribute to HF symptoms.

METHODOLOGY

This review covers published literature 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 1. The inclusion criteria for this study were as follows: Experimental and nonexperimental 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 [BMI], and smoking). The electronic databases used for this study were PubMed and CINAHL and others as noted in Figure 1; peer-reviewed journal articles were sought out using four sets of key terms as listed in Figure 1. Using the identified search terms related to HF, lifestyle factors, TMAO, TNF-α, symptom burden, diet, African Americans, 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. Equator guidelines were acknowledged using preferred reporting items for systematic reviews and meta-analyses to the degree possible and adapted for an integrative review which also included theoretical papers. Articles that were updated over time with significant new insights were included for the study. Figure 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 the recurrent themes and patterns in the literature.[23]

RESULTS

The results of this integrative review were organized into an evidence table that notes authors, research design, sample and setting, analysis, and outcomes/results [Table 1]. 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 analyses. Importantly, lower inflammatory markers were associated with lower HF symptoms.[24,25] TNF-α plays a key role in the development and exacerbation of HF and may serve as a modifiable target for lifestyle interventions.[26–29] Iron deficient persons with HF have increased levels of TNF-α in particular.[30] 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.[31] 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.[13,22,32] 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.[33–36]

More themes of evidence included TMAO as contributing to mortality in the HF population, [37–39] and an unhealthy diet with lifestyle triggering inflammatory distress and even cardiac mortality with the ingestion of highly processed carbohydrates and high fat meals.[38–41] TMAO was found to be influenced by diet and lifestyle especially with choline/carnitine rich dietary patterns.[42,43]

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.[44] Many of the studies validated the significant role dietary patterns hold in the well-being or decline of persons with HF.[15,45–49] Furthermore, many of the articles presented chronic inflammation as a main contributor to depressive symptoms in HF, and sickness behaviors (fatigue, anhedonia, and sleepiness) are present with depression in HF.[13,50] In addition, 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/As. B/As were found to have dietary differences related to lower quantities of dietary antioxidants which were linked to cardiac

events.[42,51] 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 affects every racial and ethnic group, B/As have a disproportionate prevalence of this disease along with worse outcomes.[52,69] The disparities seen in this population are directly related to the earlier onset of this diagnosis, a larger number of risk factors, poorer long-term management, and multifaceted gaps of care involving social and environmental factors.[69] Furthermore, depressive symptoms and reduced quality of life are prevalent in B/As, 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.[70] In a study of B/As and White adults with HF, B/As were found to have a higher risk (Odds Ratio, 1.19) of readmission for chest pain than White adults.[71] Hospital readmission rates for B/As 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.[70]

One contributor to worse outcomes in B/A HF patients is thought to be dietary choices. The diet of B/As in the Southeastern U.S. typically contains a high intake of fried, salty, high-sugar, and processed foods.[5] In a study involving 383 B/A 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/A women enrolled in a weight loss program were found to have low percentages that met federal guidelines for healthy diets.[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/As with HF, and thus more research is needed to better understand how cultural influences on eating habits relate to HF symptom outcomes.

Sociocultural influences on self-care have also been found to influence the symptom burden and outcomes of B/As with HF.[3] In Dickson's study of a B/A 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.[53] Individuals living with HF often experience high levels of symptoms triggered by multiple factors including activity, diet, and other comorbidities. They may identify several symptom clusters throughout their course with the disease.[53] The physical symptoms of HF are often related to the depressive symptoms seen in this population.[53,54] Hospitalizations and readmissions in the HF population are often higher in the subgroup of patients that have been concurrently diagnosed with depression.[53] According to a study by Haedtke *et al.*, persons with HF who have co-morbid depression

have a 57% increased rate of readmission.[53] The symptoms of depression in HF can easily mimic those of physical symptoms, such as fatigue, listlessness, and sleepiness;[13,53] 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.[13,54] 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.[13,55]

Inflammation and oxidative stress in heart failure

Areas to consider when targeting inflammation in HF patients and alleviating symptom burden are diet and obesity, smoking, physical activity, oxidative stress, 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.[11,72] Damage from oxidative stress, which is a buildup of free radicals in the body, may lead to several chronic disease states such as cardiovascular disease and inflammation.[56] Thus, investigation of the role of healthy lifestyle factors in inflammation and oxidative stress with 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-HF, 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.[73] 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.[57] Alcohol intake poses yet another modifiable risk factor in preventing the continued inflammatory processes associated with HF exacerbations.[58] Alcoholic cardiomyopathy has been noted as a deterrent for promoting cardioprotective effects of alcohol, and HF patients are cautioned against habitual drinking.[11,58] B/As were noted in particular to have increased heart disease, coronary artery disease in specific, if moderate drinking was a part of their lifestyle.[58] 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.[74]

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.[13,55] Dekker examined the connections between depression and HF to better clarify how these two conditions exacerbate one another in terms of specific cytokines.[55] 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.[55] 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.[75] In addition, immunological responses differed among patients having acute or chronic myocardial inflammation.[75] Many medical therapies are being examined to target inflammation in HF, and dietary approaches are being considered for this as well.[59,75]

Dietary patterns, sex differences, and inflammation

Nutritional modification in HF is considered a nonpharmacologic intervention.[60] Dietary fat, as well as general nutritional intake such as iron, may modulate the inflammatory processes and cytokines in HF.[30,59] Persons with HF who consumed more saturated and trans fats had higher levels of TNF-α in the blood.[59] 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.[10,59] Persons with HF need more guidance with dietary recommendations in terms of adequacy, potency, and portion sizes.[59] 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.[61]

Several studies also highlighted the differences of HF symptom experience between men and women.[5,61] In a study by Vishram-Nielsen, women were found to have earlier onset of cardiac disease, more nonischemic cardiomyopathy, lower jugular vein distension, and lower cardiac filling pressures than men.[62] 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.[63] 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.[64] As the symptom experience may vary between the sexes, the impact of inflammation may be different as well as their dietary patterns.[64] 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.[61] 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.[76] 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.[77] 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

TMAO is a gut microbial-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] A high-fat diet, like the one characterized by 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, dietary elements, and heart failure 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.[65,78] The nutrients choline and carnitine are found in many common foods consumed by the general population, including meat, eggs, and seafood products.[66] 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.[16,20,66] 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.[79] 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 examining chronic intake of red meats with a high fat diet showed those with this kind of meat 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 Trøseid *et al.*, TMAO, choline, and betaine, two of its precursors, were examined in relation to inflammatory measures (c-reactive protein) and metabolic measures such as BMI.[18] The end-point was all-cause mortality with anticipated mortality and identification of patients in need of heart transplants.[18] Results suggested the 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 should 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. Limitations of this review included low evidence detailing the outcomes of TMAO in different cultural backgrounds, especially for B/As with HF. Additionally, variability in the methods used across reviewed studies may have introduced bias in reporting relationships related to diet and the biological assays. Combining both evidence and theoretically based literature in the synthesis may have influenced the conclusions.

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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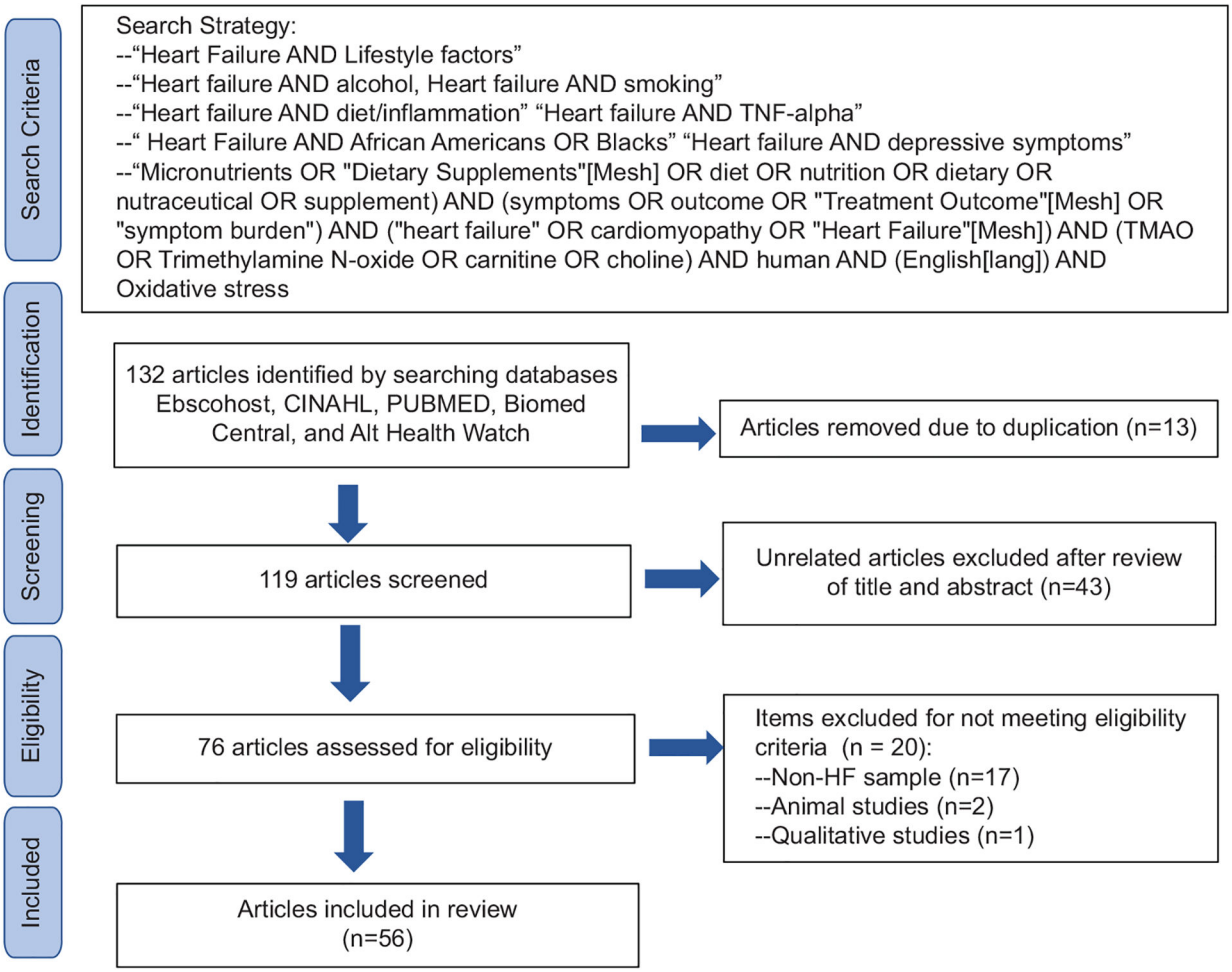

Figure 1:
Integrative literature review methodology

Table 1:

Description of the included studies

Authors	Research design	Sample and setting	Analysis	Summarized results and key relationships
Lourenço *et al.*[4]	Prospective, observation study/ cross-sectional study	125 outpatients with HF	Correlations to examine associations, nonpaired *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
Lennie *et al.*[7]	Prospective cohort study	42 HF patients	Kaplain-Meiyor 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
Lennie *et al.*[10]	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
Aggarwal *et al.*,[11]	Expert literature review	Review	NA	Diets high in red meat may increase inflammation The incidence of HF has been correlated with inflammation
Kerley[12]	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
Johansson *et al.*,[13]	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
Bianchi,[15]	Review of the literature	Review	NA	For chronic HF patients, diet is important for improvement of life quality and survival Ischemic HF patient's low oxygen availability and the use of glucose must increase
Trøseid *et al.*[18]	Observational/ prospective study	155 HF patients	Cox-regression and CIs	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
Yang *et al.*[20]	Summary of clinical evidence	Review of the clinical studies	NA	TMAO is linked with both inflammation and inflammatory biomarkers, including TNF-α
Suzuki *et al.*[21]	Secondary analysis	972 HF patients with worsening HF	CIs, 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
Ferketich *et al.*,[22]	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
Heo *et al.*[24]	Prospective, observatory quantitative study	145 HF patients recruited over 5 years	Independent *t*-tests and Chi-square tests	Patients with the lower levels of 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
Zahid *et al.*[25]	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)

Authors	Research design	Sample and setting	Analysis	Summarized results and key relationships
				The progression of HF is linked to increased pro-inflammatory cytokines, which causes inflammation TNF-α has a key role in the cause and development of HF
Shirazi *et al.*[26]	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 HF Cytokines are thought to be elevated in the state of heart disease
Murphy *et al.*[27]	Expert literature review	NA	Review	Inflammation is key in the pathophysiology of HF/targeted for therapy Sub-phenotypes should be considered for anti-inflammatory therapy with HF
Bordoni *et al.*[28]	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
Rea *et al.*[29]	Literature review	Review	NA	TNF-α was found to be elevated in postheart attack patients and increased the risk of reoccurring cardiac disease
van der Wal *et al.*[30]	Secondary analysis	2357 HF patients in the database	Chi-square, mean, SD, Mann–Whitney *U*, logistic regression and Kaplan-Meier curves	Iron deficient HF 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
Salyer *et al.*[31]	Cross-sectional study	Convenience sample: 146 patients enrolled	Frequencies, multiple regression and correlations	Factors that impact HF symptoms as related to nutrition include socioemotional factors, appetite/hunger and illness related factors The sickness behavior symptom cluster influenced quality of life in a negative manner
Seongkum *et al.*[32]	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
Angermann and Ertl[33]	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 *et al.*[34]	Literature review	NA	Review	Poor medical and functional outcomes have been linked to depression and anxiety in HF
Alpert *et al.*[35]	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
Eastwood *et al.*[36]	Secondary analysis from the HF health related quality of life registry	622 HF patients, 18 years old and older	ANOVA analyses and Chi-square models	Depressive symptoms in men and women 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
Suzuki *et al.*[37]	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

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Authors	Research design	Sample and setting	Analysis	Summarized results and key relationships
Rahman *et al.*[38]	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 *et al.*[39]	Literature review	Review of the literature	NA	TMAO levels are higher in HF patients as compared with healthy populations, linked to NYHA grades, ischemic HF and morbid outcomes
Serafini and Peluso[40]	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
Zinöcker and Lindseth[41]	Expert literature review	Literature review	NA	The Western diet is linked to inflammation that is derived from structural and behavioral changes in the resident microbiome
Yazaki *et al.*[42]	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
Heianza *et al.*[43]	Meta-analysis and expert review	Review of prospective studies with cardiac population	CIs and relative risks	TMAO, in higher concentrations of the blood is linked to cardiac events Increased intake of phosphatidylcholine is linked with more CVD risk/mortality Increased TMAO contributes to atherosclerosis
Mathew *et al.*[44]	Cohort study	13 hypertensive patients with HF	Logistic regression and correlations	Dietary changes with low sodium measures showed metabolite changes-improved energy utilization (among carnitines and amino acids
Miró *et al.*[45]	Prospective cohort study	991 patients	CIs and hazard ratios	The Mediterranean diet was linked to decreased rates of hospitalization. Although not correlated with long-term mortality
Kumar *et al.*[46]	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
Abshire *et al.*[47]	Literature review	Review	NA	A low sodium diet may be harmful for HF populations
Butler[48]	Expert review	Review	NA	There are a lack of 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
Freedland[49]	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
Leonard[50]	Expert review	NA	Literature review	Chronic inflammation may contribute to depression Sickness behaviors are present with depression and may also be distinct from it
Wu *et* al.[51]	Secondary analysis	247 African American HF patients	Cox regression analyses	African American patients had more diets with less antioxidants Antioxidant diets are linked to more cardiac event-free survival
Haedtke et al.[53]	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 noncardiac 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
Chapa *et al.*[54]	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

Authors	Research design	Sample and setting	Analysis	Summarized results and key relationships
Dekker *et al.*[55]	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
Brancaccio *et al.*[56]	Expert review	NA	Review	Healthy lifestyle factors such as dietary supplements that counteract oxidative stress can also prevent further cardiac disease
Siasos *et al.*[57]	Literature review	Review	NA	Smoking is also an identified risk factor linked to vascular inflammation and should be considered in the study of HF patients and symptom burden
Rohde and Beck-da-Silva[58]	Editorial review	Evidence review	NA	Alcoholic cardiomyopathy has been noted as a deterrent for promoting any cardioprotective effects of alcohol and HF patients should be especially cautious with engaging with habitual drinking
Payne-Emerson and Lennie[59]	Expert review	Review of guidelines in HF	NA	Inflammation influences nutrition requirements in HF Dietary fat affects the inflammation process in HF
Kuehneman *et al.*[60]	Summarized review of the literature for expert work	Review of the literature	NA	Nutrition in the treatment of HF is considered a nonpharmacological intervention Optimal nutritional management can reduce admissions and mortality
Lennie *et al.*[61]	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
Vishram-Nielsen *et al.*[62]	Retrospective study	429 HF patients	Kaplain-Meier, Cox-hazard analysis, log-rank tests	Female survival rates were higher Less deranged hemodynamics were found in women
Dewan *et al.*[63]	Cohort study	15,415 HF participants	Hazard ratios	Women had higher blood pressure, more obesity, higher heart rate Women had higher emotional symptoms
Lee *et al.*[64]	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
Tang *et al.*[65]	Review of the literature	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
Ufnal and Nowiński[66]	Review of literature	Review	NA	TMAO has a negative impact on cardiac events and coronary artery events
Shivappa *et al.*[67]	Meta-analysis	HF study populations	Odds and hazards ratios, relative risks	The pro-inflammatory diet is linked with increased CVD mortality
Song *et al.*[68]	Cohort study	177 HF patients	Linear and Cox regressions	Vitamin D deficiency predicted more cardiac events
Sharma *et al.*[70]	Cohort study	80% African Americans with HF	Univariate and multivariate analyses	Higher burden of depressive symptoms in HF led to higher prevalence of functional impairment

sTNFR1: Solid tumor necrosis factor receptor 1, NA: Not available, HF: Heart failure, TNF: Tumor necrosis factor-α, CIs: Confidence intervals, SD: Standard deviation, CVD: Cardiovascular disease, TMAO: Trimethylamine-N-Oxide, NYHA: New York Heart Association, BNP: B-type natriuretic peptide, LVEF: Left ventricular ejection fraction