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Biological mechanisms underlying widowhood's health consequences: Does diet play a role?

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ABSTRACT

The loss of a spouse is a highly stressful event that puts older adults at increased risk for morbidity and mortality. The risk is highest in the first year to 18 months post-loss; nevertheless, widow(er)s, in general, are at heightened risk of cardiovascular disease (CVD) related morbidity and mortality, and to a lesser extent, non-CVD related morbidity and mortality. The primary goal of this article is to argue for a perspective that considers diet and emotion-induced autonomic, neuroendocrine, and immune dysregulation, in unison, to understand the mechanisms underlying morbidity and mortality in early widowhood. Toward this end, we first summarize our previously published work, as well as work from other investigatory teams, showing that compared with those who were not bereaved, widow(er)s have higher levels of pro-inflammatory cytokine production and more dysregulated autonomic and neuroendocrine activity than non-widow(er)s, independent of health behaviors such as diet. We highlight that a major gap in our current understanding of the biobehavioral mechanisms that underlie the widowhood effect is the role of diet and hypothesize that the adverse health impact of grief and associated negative emotions and diet may be more than additive. Therefore, we propose that diet may be a pathway by which widow(er)s are at higher CVD risk requiring further investigation.

Stressful life events and the negative emotions they engender increase the risk of morbidity and mortality in older adulthood [1]. Older adults are confronted with several major life stressors. Chief among these is when a spouse becomes chronically ill or dies. Predominantly experienced in older adulthood, a spouse's death ranks first on the social readjustment scale [2]. Although most widow(er)s do not require psychotherapeutic treatment for grief or depression after the death of a spouse, widow(er)s are confronted with a set of novel daily stressors related to the loss (grief-related) and connected to role changes as a result of the loss (restoration-related stressors) [3]. Accordingly, widowhood is characterized by grief, depression, and stress for some older adults. These stressors impact physical health and quality of life [1].

The "widowhood effect," the heightened likelihood of a widow(er) dying a relatively short time after his or her long-time spouse has died, is among the most recognized illustrations of how stressful life events impact morbidity and mortality in behavioral medicine and the broader society [4,5]. When considering the widowhood effect at a population level, preventing CVD-related and non-CVD-related morbidity in mortality in widow(er)s is significant.

Precise estimates of the "widowhood effect" vary. Consider one study showing that widow(er)s had 61% greater odds of death in the first 6 months of widowhood and 18% greater odds of death in the first two years of widowhood than when married [1]. In comparison, over one year, if someone over the age of 65 took statins, they would have 42% lower odds of death than if they did not. In another study of 30,447 individuals aged 60–90 years of age, widow(er)s had a 25% higher mortality risk in the first year post-loss [6]. Two meta-analyses determined the "widowhood effect" is responsible for a 30–90% increased risk of mortality in the first six months and a 15% risk afterward [4,5].

Widow(er)s are at increased risk of morbidity and mortality nearer to the time of the loss; however, data from 15,935 US older adults enrolled in the health and retirement study showed that widow(er)s are at 48% greater risk of morbidity and mortality compared with married and never married people [1]. Cardiovascular-related morbidity and mortality was the most common cause of morbidity and mortality in widow(er)s, as it is in the broader bereavement literature. In a large study of 373,189 older American couples, researchers found that widowhood

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was related to mortality at higher rates for males than females; nevertheless, the risk was substantial for both [4]; notably, the risk for CVD-related morbidity and mortality existed for both husbands and wives. The effect was equivalent or exceeded CVD's established risk factors for ischemic heart disease, congestive heart failure, cerebral vascular accident or stroke, and other heart or vascular diseases [4].

Given the links between widowhood and physical health, especially concerning CVD, it is critical to understand the factors that contribute to widowhood-related morbidity and mortality. The primary goal of this article is to argue for a perspective that considers diet and emotion-induced autonomic, neuroendocrine, and immune dysregulation in unison to understand the mechanisms underlying morbidity and mortality in early widowhood. We present our conceptual framework in Fig. 1. As can be seen on the lower left-hand side of our conceptual model, Path A illustrates that significant post-loss negative emotions (i.e., symptoms of grief, depression, and stress) can dysregulate autonomic, neuroendocrine, and immune function in ways that promote disease risks [7]. Path B is based on our contention that these same negative emotions make widow(er)s more likely to consume comfort foods and fast-food type meals.

There is good evidence to suggest that grief (as well as stress and depression) may potentiate the adverse repercussions of eating high saturated fat comfort foods because the postprandial (post-meal) response of lipids and pro-inflammatory cytokines are exaggerated– as a result of stressful life events and the negative emotions they generate. Thus, Path C indicates that unhealthy comfort foods and fast-food type meals may be more detrimental to a widow(er) 's physical health among widow(er)s with more symptoms of grief, stress, and depression. As can be seen in Path D, we hypothesize widow(er)s with a mood disorder history will be more likely to consume comfort foods and fast-food type meals after the death of their spouse; they will also be more likely to experience adverse health outcomes as a result.

We commence by reviewing the literature comparing bereaved adults to nonbereaved adults. As will be evident, there is general agreement that those who are bereaved exhibit dysregulation of multiple bodily symptoms (e.g., autonomic, neuroendocrine, and immune). Then, we will review the evidence for our model and provide a research agenda for future work. A key argument in this paper is that diet, and negative emotions have independent and synergistic effects for morbidity and mortality among widow(er)s. Evidence for this scientific premise will be reviewed in the latter half of this paper. Nevertheless, we encourage the reader to consider the implications of this assumption for theoretical and intervention purposes throughout.

Autonomic Activity. Stress hormones, which are elevated in widow(er)s, are an important indicator of CVD risk. When the stress response system is activated, catecholamines are released as part of the sympathetic nervous system response, which increases blood pressure, heart rate, and stress cardiomyopathy. Norepinephrine-dependent adrenergic stimulation also triggers nuclear factor kappa-B (NF-kB). This intracellular signaling molecule regulates pro-inflammatory cytokine gene expression [8]. Widowhood is associated with elevated urinary catecholamines and hypertension. Bereavement has also been linked to elevated catecholamines and higher blood pressure [9,10].

Stress and depression dampen vagally mediated heart rate variability (HRV), an index of parasympathetic function, predictive of CVD-related morbidity and mortality [11,12]. The mechanisms by which lower vagally mediated HRV boosts CVD risk, heart attack, and CVD-related mortality are multifactorial [13]. The vagus nerve innervates the heart's sinoatrial node (i.e., the heart's pacemaker). It can modulate rapid heart rate fluctuations to restore normal function. Low vagally mediated HRV, is also inversely associated with hypertension, diabetes, and lower high-density lipoprotein (HDL), even after accounting for age, BMI, smoking, and alcohol consumption [14,15]. Via the cholinergic anti-inflammatory pathway, parasympathetic activity (indexed by lower HRV) is inversely related to pro-inflammatory production, another mechanism that may underlie CVD risk in widow(er)s as described in

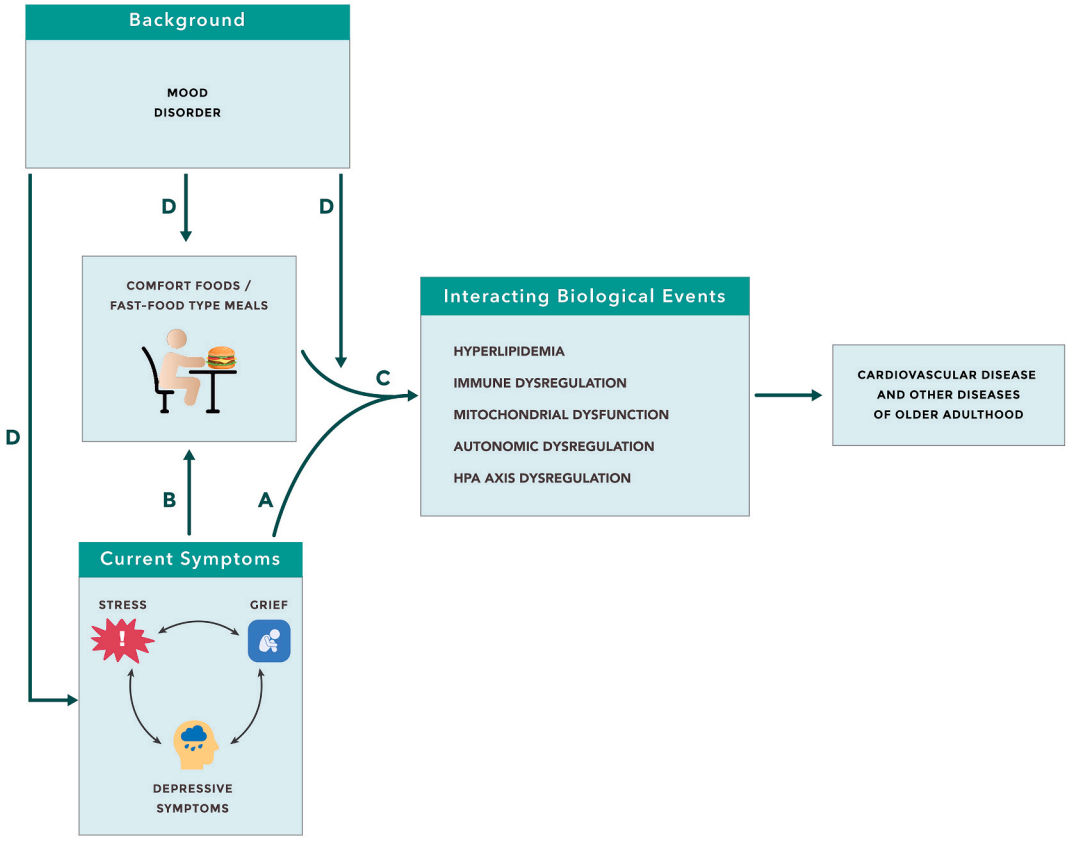

Fig. 1. Conceptual model linking diet and symptoms of grief, stress, and depression to adverse health outcomes.

more detail below [16].

Our recent work showed that widow(er)s had lower vagally mediated heart rate variability than matched comparisons within the first six months post-loss [17]. Although there is an established link between health behaviors and HRV, our finding persisted independent of health behaviors. Bereaved adults who exhibited more depressive symptoms had lower HRV than widow(er)s who reported less depressive symptoms, illustrating that even in a population of older adults who recently experienced a significant life stressor, there is an inverse relationship between depressive symptoms and HRV [10].

Neuroendocrine Activity. Some widow(er)s exhibit prolonged elevated cortisol production. Elevated morning cortisol levels have been linked to higher plasma glucose and higher blood pressure [18], while the degree to which cortisol increases as a result of a psychological stressor was associated with the amount of plaque calcified in the arteries [19]. This calcium buildup in the coronary arteries, measured by computed tomography of the heart, is a better predictor of heart attack than cholesterol screening and other standard risk factors [20]. Although cortisol is anti-inflammatory, chronically elevated cortisol production can desensitize immune cells to the anti-inflammatory properties of cortisol, thereby allowing pro-inflammatory cytokines to be produced in an unregulated environment. A recent systematic review of neuroendocrine activity and bereavement concluded that widow(er)s had elevated mean cortisol levels than matched nonbereaved individuals [21]. Notably, most of this work does not exclusively focus on widow(er)s [21].

Inflammation. Pro-inflammatory cytokines are signaling molecules released from immune cells that are responsible for both local and systemic inflammation. Stress and depression boost inflammation, which is a significant factor underlying cardiovascular-related morbidity and mortality. Pro-inflammatory cytokine production is associated with incident coronary heart disease (CHD), acute coronary syndrome (heart attack and unstable angina), fatal coronary heart disease, and all-cause mortality [22].

Knowles, Ruiz, and O'Connor recently wrote an excellent review of 41 years of research on bereavement and immune dysregulation [23]. Related to CVD, they identified three studies that detected differences between bereaved and nonbereaved adults' cytokine levels; these papers showed that markers of circulating pro-inflammatory cytokines, measured in serum or plasma, are higher among bereaved than matched comparisons [24–26]. Although only one of these studies included widow(er)s only [26], these studies demonstrate that bereavement consistently has a powerful impact on the inflammatory network. Of note, elevations in IL-6 were reliably higher, showing the most prominent effect as an inflammatory index in all three studies.

1. Path A: negative emotions and physiological dysregulation among Widow(er)s

Although a population of widow(er)s will, on average, have a more dysregulated autonomic, neuroendocrine, and immune system than those who are not widowed, our model suggests meaningful stress-induced differences in neuroendocrine and immune activity within widow(er)s (Path A). Compared to those with average levels of grief, participants with complicated grief, a former psychiatric diagnosis, show lower morning cortisol levels and a flatter cortisol slope across the day, two indicators of dysregulated neuroendocrine function [27]. Notably, chronic secretion of cortisol impairs immune cell's ability to kill pathogens [28]; furthermore, although usually anti-inflammatory, chronically elevated cortisol levels can *sometimes* promote glucocorticoid insensitivity, thereby raising systemic pro-inflammatory cytokines in the periphery [29]. Our team recently examined between-person differences among widow(er)s in terms of pro-inflammatory cytokine production. Following Path A (Fig. 1), individuals with higher grief severity had a greater production of pro-inflammatory cytokines than those with less grief severity; widow(er)s who reported more significant depressive symptoms exhibited greater pro-inflammatory cytokine production compared with those who had lower depressive symptoms [30].

2. Path B: negative emotions and dietary choices among Widow (er)s

We assert that widow(er)s who experience elevated symptoms of grief, depression, and psychological stress will be more likely to consume comfort foods and fast-food type meals (Path B). There is a dearth of empirical research on grief and dietary choices; the basis for Path B comes from (a) a rich theoretical tradition on loss and food that descends from the psychoanalytic tradition, (b) qualitative research on grief and diet, and (c) mechanistic psychobiological research on mood and food.

Classical theories within the psychodynamic tradition suggest that unhealthy dietary habits and overeating behaviors symbolize "emotional nurturance" [31,32]. According to psychodynamic theory, eating unhealthy comfort foods, in times of social isolation and loneliness, can serve as a "transitional object," a surrogate form of security ideally provided by close relationships [33]. In the context of bereavement, comfort foods may serve as a temporary replacement for the void some widow(er)s experience [34].

Preliminary data on grief & diet. Widowhood has been linked to poorer quality diet in the first two years post-loss; however, the data is severely limited and primarily cross-sectional [35]). In one study, 50 widow(er)s and 50 married comparisons were interviewed about their eating behaviors and emotional well-being; they also recorded their diet intake for 3 days using the Food Frequency Questionnaire [36]. Results indicated that after a spouse's death, the social meaning of eating is negatively altered, which may have explained the adverse effects on substandard nutrient intake. Thirty older adults ranging in age from 63 to 90 years of age (17 widow(er) engaged in a semi-structured focus group discussion (4–10 older adults in each group) on food choice and changes in food preferences using open-ended, focused but not leading questions. Using an inductive coding and thematic analysis approach for qualitative data analysis, the researchers concluded that both male and female widow(er)s discussed making unhealthy food choices (e.g., higher consumption of high saturated fat meals and sugar) [37]. In another study, 15 widows (i.e., all women widow(er)s) engaged in one-on-one interviews 6 months and 15 months after their spouse's death. Using constructiveness grounded theory to evaluate this data, results indicated that widow(er)s feel less motivated to prepare meals because they lack the commensality used to accompany eating [38]. Similar patterns of qualitative data have been underscored from other qualitative investigations [39,40]. Qualitative interviews conducted on 31 widow(er)s were coded using a thematic approach; results revealed widow(er)s perceive eating alone as "problematic" [39].

There have been a few empirical studies that have investigated a potential link between widowhood and diet. An empirical study of 58 recently widowed older adults and 58 age-matched married comparisons evaluated food intake using the Food Frequency Questionnaire; the widow(er)s ate twice as many commercial meals weekly compared with married participants [41]. In another empirical study that consisted of 15 older adults who were widowed in the past year, 7 married older adults, and 7 that used the determine checklist to evaluate nutritional intake, widow(er)s had a nutrition deficit score that was over twice as high as married older adults [40]. Not surprisingly, widow(er)s ate more commercial fast-food type meals than others [42,43]. In a larger study of 38,865 individual, those who were widowed or divorced, reported less vegetable consumption as measured with the Food Frequency Questionnaire [42]. Of course, the cross-sectional design of the aforementioned studies limits causal inference. In addition, we know of no study that has examined pre-loss dietary patterns, in addition to post-loss nutritional patterns.

Biological mechanisms underlying emotions and eating

behaviors. Eating behaviors are regulated by two interacting systems that act in parallel. The homeostatic system includes hormones, such as leptin, ghrelin, and Insulin, that regulate hunger by acting on the hypothalamic-pituitary-adrenal (HPA) axis and brain stem. The reward system, consisting of dopamine-producing neurons in the ventral tegmental area (VTA), communicates with neurons in the nucleus accumbens to facilitate reward [44].

Neuroendocrine hormones released from the HPA axis modulate appetitive functions during acute and chronic stress conditions. Under acute stress, the corticotropin-releasing hormone, which initiates a cascade of events leading to the release of glucocorticoids (e.g., cortisol), also suppresses appetite via its influence on various regions in the hypothalamus and bed nucleus of the stria terminalis [45]. In contrast, elevated glucocorticoid levels during ongoing chronic stressors (e.g., bereavement) stimulate food intake by influencing appetite-regulatory hormones such as Insulin, leptin, and ghrelin [45]. For example, Insulin typically reduces food intake by acting on the hypothalamus and reduces the rewarding nature of food by influencing dopaminergic-mediated neuronal activity in the ventral tegmental area [46]. Acute increases in glucocorticoid levels stimulate insulin secretion from the pancreas, thereby suppressing appetite. In contrast, chronically elevated glucocorticoid levels contribute to insulin resistance, which reduces the appetite-suppressing effects of Insulin on the hypothalamus.

Psychological stress and depression boost the desire to eat high-fat comfort foods and fast-food type meals; foods high in saturated fat temporarily reduce feelings of sadness and depression, which may be why grief eating is a cross-cultural phenomenon [47]. When exposed to an experimental stressor, those who secreted more cortisol ate more high fat and sugar foods than those who were not exposed to the stressor. Other studies that administered glucocorticoids through injection also showed that people were more likely to desire high-fat or sweet foods after the injection than before [48].

Highly palatable foods that are high in sugar and fat (e.g., comfort foods) decrease stress and temporarily improve mood [49]. Mechanistically, Insulin's suppressive effects on reward pathways may contribute to craving high-reward foods under stressful conditions to achieve the same rewarding effect [45]. Indeed, multiple studies on rats and monkeys have shown that exposure to a social stressor can induce hyperphagia (i.e., the intense desire to eat) of energy-dense foods [50]. In rats, highly palatable foods reduce activity in the central stress response (i.e., adrenocorticotropic hormone, glucocorticoids) [51], which suggests consuming rewarding food can reduce stress. In addition, dopamine in the mesolimbic area (i.e., nucleus accumbens and ventral tegmental area) is boosted when comfort foods are consumed [44]. In a provocative well-designed experimental study, participants' stomachs were injected with either saline or fat; then, they were exposed to sad images and music. Those who were in the "high-fat condition (i.e., injected with fat) were 50% less impacted by the sad images and sad music than those in the control condition (i.e., injected with saline) [47].

Eating behavior changes and the physiological and psychological distress associated with spousal loss may be attributed, in part, to underlying alterations in the endogenous opioid system. Endogenous opioids and their receptors are located throughout the central, peripheral, and autonomic nervous systems. The widespread distribution of the endogenous opioid system parallels its broad range of functions, including social attachment, reinforcement and reward processing, and autonomic and neuroendocrine regulation [52]. Extensive animal research and preliminary work in humans highlight the involvement of endogenous opioids in prosocial behavior [52,53]. Endogenous opioids are also implicated in eating behavior; in general, endogenous opioid agonists increase food intake while endogenous opioid antagonists decrease food intake [54]. Endogenous opioids also mediate, modulate, and regulate neuroendocrine, autonomic, and behavioral stress responses [55].

Maladaptive grief patterns can be conceptualized as disorders of reward [56,57]. Close bonds provide security, sustain pleasure and reward, and attenuate sympathetic-driven processes and promote parasympathetic activity; conversely, loss of close social bonds dysregulates reward circuitry and related biobehavioral systems [58]. While speculative, changes in appetitive behavior following bereavement may respond to adaptations occurring between biobehavioral systems and the endogenous opioid system. Consumption of "comfort foods" may provide temporary pleasure and reduce psychological stress, but chronic consumption of high-fat foods may instill maladaptive neurobiological and neuroendocrine patterns that jeopardize long-term health.

3. Path C: health consequences of comfort foods & fast-food type meals

Comfort foods and pre-made fast food type meals are generally high in saturated fat, sugar, and often *trans*-fat. Starchy foods and sugar-filled candies boost glucose, which triggers transcription factor NF-kB [59] regulating aspects of the innate and adaptive immune systems, and stimulates pro-inflammatory gene expression [60]. By activating NF-κB, glucose activates pro-inflammatory genes and adhesion molecules that lead to the adhesion of monocytes to endothelial cells [61]. When people eat high saturated fat diets, LPS uptake in the gut is boosted, which can trigger low-grade systemic inflammation and insulin resistance [62]. Saturated fatty acids activate adipose tissue to produce an inflammatory response by triggering toll-like receptors, which bind to LPS (a natural TLR-4 ligand); thus, promoting an innate immune response by stimulating monocytes and macrophages [59,63]. TL-4 also impacts various aspects of the adaptive immune response. When TLR-4 on macrophages and adipocytes are triggered, they facilitate translocation of NF-κB to the nucleus [64,65]), which inhibits insulin signaling and increases insulin resistance [66].

Low-density lipoprotein cholesterol (LDL), very-low-density lipoprotein (VLDL), and triglycerides promote fatty buildup in the blood vessel wall, which narrows as a result. Through this process, elevated LDL and triglycerides play a significant role in atherosclerosis; triglycerides also contribute to atherosclerosis by stimulating pro-inflammatory cytokine production [67]. Non-fasting triglycerides are strongly associated with myocardial infarction, ischemic heart disease, cardiovascular events, and cardiovascular death. Multiple studies have shown that postprandial lipid levels, especially triglyceride levels (hypertriglyceridemia), predict CVD-related morbidity and mortality better than fasted levels. In the Women's health study, 26,509 healthy women were followed over 11 years to detect cardiovascular events and cardiovascular death.

Both fasting and postprandial triglyceride levels predicted cardiovascular events; triglyceride levels were more reliably associated with cardiovascular events when assessed in a postprandial state than a fasted state [68]. In the Copenhagen City Heart Study, 7587 women and 6394 men were followed for approximately three decades; postprandial triglycerides were prognostic for future CVD events and premature mortality for both sexes [69]. In a study of 101 males (61 with coronary heart disease and 40 without), postprandial triglyceride levels predicted CAD's presence (assessed by coronary angiography) better than fasting levels [70]. Notably, among those who were overweight, postprandial responses were particularly prognostic of CAD.

A high saturated fat meal induces transient increases in blood triglycerides (postprandial hyperlipidemia) by increasing triglyceride-rich lipoproteins, including chylomicrons, and very low-density lipoproteins (i.e., the primary lipid carrier of triglycerides). Postprandial hyperlipidemia enhances immune cell count for up to 8 h after consuming a high saturated fat meal. Through direct interaction with triglyceride-rich lipoproteins, foam cells are formed in atherosclerotic lesions in the arterial wall, an important aspect of atherosclerosis (described above).

Triglycerides also provoke monocytes to produce pro-inflammatory cytokines. For example, one study showed that postprandial hyperlipidemia led to a 10-fold increase in the pro-inflammatory cytokine, TNF-α, within human aortic endothelial cells (i.e., the layer of squamous cells

that line the interior of the largest artery in the heart) [71]. Multiple labs have shown IL-6, TNF-alpha, and CRP increase following a single meal high in saturated fat [72].

The calcium buildup (plaque) in the coronary arteries are better predictors of heart attack than cholesterol screening and other standard risk factors [20]. Increased postprandial levels of VLDLs and triglycerides promote coronary artery calcification, a measure of calcium-containing plaque in the arteries that can restrict blood flow to the muscles in the heart. Prolonged postprandial triglyceride responses are reliably associated with enhanced artery calcification [73].

4. High saturated fat meals & grief: a dangerous combination?

A significant gap in our current understanding of the biobehavioral mechanisms that underlie the widowhood effect is how the stressors associated with bereavement interact with dietary behaviors. We hypothesize that the adverse health impact of stress and stress and diet is synergistic rather than additive (represented in Fig. 1 when Path A and Path C merge). Psychological stress and depression can promote lipemia (presence of high lipid content in the blood) by enhancing triglyceride responses to a high saturated fat meal and inhibiting clearance [74]. In one study, total triacylglycerol (TG) and very low-density-lipoprotein-TG areas under the curve were 50% or higher during a stressful condition than a control condition [75]. This finding was not related to pre-meal levels. Increased postprandial changes were independent of baseline triacylglycerol levels [75]. In another study, acute stress also slowed triglyceride clearance [76]. Compared to the non-stress session, clearance of an exogenous fat load took 14% longer on average following a laboratory stressor [76]. In another study, participants were provided the same 4,186 kg meal consisting of bread, butter, ham, apple marmalade, and cottage cheese across two visits. In one visit, participants repeatedly engaged in a mental stressor designed to elicit a stress response. On the other visit, they completed a benign keyboard task. Postprandial VLDL triglycerides were higher during the stress condition than the non-stress condition; furthermore, VLDL-cholesterol response, calculated as the area under the curve, was higher during the mental task than during the control sessions [75].

Given that chronic stress primes the stress-response system subsequent acute stressors, widow(er)s may be more vulnerable to the negative postprandial impact of unhealthy foods high in fat and sugar in the context of everyday stressors. Mechanistically, the elevated levels of catecholamine's among widow(er)s, compared with others, mediate this association [76]. In another study, a bolus dose of fat was injected in participants twice over two separate visits; one visit included a series of experimental stressors while the fat was being digested. Triglycerides took longer to clear in the stress condition than in the non-stress condition [76]. Importantly, males and postmenopausal females appear to exhibit the highest stress-induced lipid response; widow(er)s are almost entirely in this demographic [74,77].

Psychological stress can promote postprandial inflammatory response through multiple pathways. Triglycerides, which are elevated under psychological stress, boost inflammation. As described above, high-fat meals can increase bacterial endotoxemia, which stimulates NF-kB in leukocytes [78,79]. Similar to when LPS stimulates peripheral blood mononuclear cells, comfort food-type meals may prime immune cells to be more responsive to psychological stress.

Inflammation promotes mitochondria dysfunction, which is now recognized as one of the key mediators in cardiac disease's pathophysiology ([80]. The cost of chronically producing cytokines, the clinically relevant markers, happens during chronic low-grade inflammation, which ultimately causes changes in the metabolism of the immune cells and leading to a decrease in oxygen consumptions and energy production in the form of adenosine triphosphate(ATP) [81]. In turn, mitochondria dysfunction can autonomously trigger stress-induced physiological responses such as SAM hyperactivation [82], peripheral insulin resistance leading to hyperglycemia and metabolic syndrome [82], and inflammation [83].

5. Path D: mood disorders as moderators

As can been seen in the pathway labeled D on the left-hand side of Fig. 1, we hypothesize that widow(er)s with a mood disorder history will be more likely to consume comfort foods and fast food type meals than those without a mood disorder history; they will exhibit more symptoms of stress, grief, and depression. We propose a synergistic relationship between a mood disorder history and the consumption of high saturated fat foods, as shown in the middle of Fig. 1 when Path D converges with Path C.

Mood disorders, such as major depression, have a complex multifactorial etiology and bidirectional associations with disturbances in autonomic, neuroendocrine, immune, and mitochondria function [84]. A history of a mood disorder (particularly major depressive disorder, the most common mood disorder) is associated with morbidity and mortality, with CVD being the most common [85]. A history of mood disorders sensitizes the inflammatory stress response. Even without being in an active episode, those with a mood disorder have greater emotional and physiological reactivity to stressors than those without a mood disorder history [86,87]. This physiological profile may put widow(er)s with a history of mood disorders at heightened risk for CVD and other adverse health-related outcomes if high saturated fat foods are consumed excessively. In a food challenge study to examine the impact of mood disorders on postprandial responses to a high saturated fat meal, IL-6 increased among those with a history of major depression at a higher rate than those without a depression history [88]. In the same study, those with a history of mood disorders who also experienced more recent stressors had a robust postprandial triglyceride response to a high saturated fat breakfast that persisted throughout the day than those without a mood disorder history.

The "scarring hypothesis" suggests that a history of a mood disorder produces long-term cognitive, emotional, and behavioral changes that make people more vulnerable during stressful life events such as a spouse's death [89]. A history of mood disorders boosts emotional vulnerability to stress, unhealthy dietary choices, and binge eating [90]. Notably, the link between diet and mood is likely bidirectional. High fat, low-complex carbohydrate diets may boost the risk of an active episode among those with a mood disorder history; accordingly, the consumption of comfort foods and fast-food type meals may increase the risk of severe depression and grief in the context of spousal loss.

6. Additional moderators and future directions

Gender Differences. Gender differences in eating-related activities may partially explain the gender differences in post-bereavement mortality rates reported by Elwert & Christakis [4]. Being widowed is associated with lower fruit and vegetable variety intake, especially for men [91]. Cooking skills negatively correlate with energy intake [92]. Because women traditionally engage in cooking activities, bereaved men may be unprepared to start this role in older adulthood and, instead, resort to quick and simple meals at the expense of a nutritious diet. Social relationships influence dietary habits, and widowed men may be particularly vulnerable to these effects. Widowed men are at greater risk for social isolation and loneliness compared to widowed women [93], who tend to have more extensive social networks, report more frequent contact with friends during the week [94], and experience increases in social network size during the first 4 years of widowhood [95]. In general, greater participation in social activities is associated with better diet quality in older men and women [96]. Not surprisingly, living alone or infrequent contact with friends exaggerate the relationship between being widowed and lower fruit and vegetable variety consumption [91]. Taken together, diet, gender, and social integration interact dynamically to influence post-bereavement health outcomes. Ecological momentary assessment paired with complex

statistical modeling will be necessary to capture how stress and socio-environmental factors influence day-to-day health patterns and long-term health trajectories in widowhood.

Context. Diet is understudied within the context of spousal caregiving, another avenue for future research. Spousal caregiving is a robust predictor of cardiovascular disease [97]. The association between inflammation and AD spousal caregivers is well described [98]. Caregiving for a spouse with Alzheimer's disease (AD) is one of the most stressful experiences a person can encounter, and has been characterized in terms of a living bereavement [99]. On average, AD spousal caregivers spend more than 10 h per day providing care [100]. A recent cross-sectional study suggests that caregivers may lack dietary nutrients, and hours of caregiving contribute significantly to health behavior choices [101]. The median survival time for AD spousal caregivers is between 3.3 and 11.7 years, making this a chronic stressor with considerable caregiver burden [102]. In addition to the stress associated with around-the-clock care, AD spousal caregivers experience grief and other psychological reactions typical of those who have been widowed [103]. It is well documented that AD spousal caregivers report poorer quality of life (QOL) than non-caregivers. Not surprisingly, AD spousal caregivers are at risk for mental and physical health problems, as well as early mortality [102]. Other caregiving contexts may also be relevant. For example, spousal caregiving for cancer patients is associated with CVD and stroke [104]. Diet may play a critical role in the association between caregiving and CVD as well.

In some cases, diet changes after spousal loss may facilitate or parallel health recovery in spousal caregivers. For the average spousal caregiver, bereavement represents a turning point—health declines as bereavement approaches but rebounds after spousal death [105]. No study to date has examined how diet changes from pre-to post--bereavement in spousal caregivers. More longitudinal studies like the Wilson et al. [105] study are necessary to determine if and how health behaviors influence pre-to post-bereavement changes in health.

7. Conclusion

The field of Psychoneuroendocrinology has made considerable progress toward understanding how stress-induced dysregulation underlies the "widowhood effect." Research on how diet and grief-related physiological dysregulation interact has not been explored, but it should be. More broadly, except for a growing literature on sleep and dysregulated immunity in widowhood [106], there is no work, to our knowledge, that has examined how health behaviors interact with stress-induced autonomic, neuroendocrine, and immune alterations in a population of widow(er)s. Understanding the stress-response system's health impact, independent of health behaviors, limits real-world applicability. A transdisciplinary research effort is needed to create new methodological approaches that ultimately generate translational innovations.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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