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Mediterranean Diet and Fatigue among Community-Dwelling Postmenopausal Women

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A dissertation

Submitted in partial fulfillment of the

Requirement for the degree of

Doctor of Philosophy

University of Washington

2022

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Program Authorized to Offer Degree:

School of Nursing

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## University of Washington

### Abstract

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### Abstract

#### Background

Fatigue is one of the most common yet unexplained complaints in the primary care setting. Fatigue was related to an accelerated decline in mobility and cognitive function and the risk of hospitalization. Declined function and hospitalization were among the strongest predictors of transitioning from the community to residential care settings or nursing homes. Yet, fatigue in community-dwelling older adults has been underrecognized because of poor assessment and management. Physiologically, fatigue is the result of increased inflammation, increased oxidative stress, lack of essential nutrients, and altered metabolism. The Mediterranean diet has the benefits of decreasing inflammation, decreasing oxidative stress, providing multiple nutrients such as phytochemical nutrients, and improving metabolism such as increasing insulin sensitivity and lowering LDL. Thus, a Mediterranean diet offers a possible avenue to lower fatigue, but the role of the Mediterranean diet pattern has yet to be examined in relation to fatigue, especially

while leveraging well-powered cohorts with validated dietary measures. Besides, due to the low awareness of methods used to study nutrition, advanced and novel perspectives might offer additional tools for researchers in nursing science. One method that provides such a unique perspective is the isocaloric substitution method. Using this method, nursing researchers can look holistically at the relationship between fatigue and Mediterranean diets considering ecologically sensible tradeoffs rather than general associations.

### **Objectives**

First, we reviewed definitions, measures, related factors, and consequences of fatigue in community-dwelling older adults. Second, we introduced the isocaloric substitution method to nursing research with both food and nutrient substitution as exemplars. Third, we 1) explored how the Mediterranean diet uniquely relates to fatigue and 2) examined how substituting Mediterranean diet recommended foods for Mediterranean diet not recommended foods relate to improvements in fatigue by using the isocaloric substitution method.

### **Methods**

The study used an observational cross-sectional design with participants from two ancillary studies of the Women's Health Initiative Long Life Study (WHILLS): Objective Physical Activity and Cardiovascular Disease Health (OPACH) Study and WHI-Food Intake (WHI-FI). The final analytical sample size is 4563. Four types of isocaloric substitution methods were demonstrated to examine the tradeoffs between different food choices/macronutrients. Finally, isocaloric substitution models were estimated to quantify the tradeoff in substituting foods recommended by the Mediterranean diet for foods not recommended by the Mediterranean diet (i.e., fish for red and processed meat, whole grain for non-whole grain, and whole fruit for fruit juices).

## **Results**

The results showed alternate Mediterranean Diet (aMED) Quantile 5 (Q5, the highest adherence) was associated with 2.99 (95% CI: 0.88, 5.11), 4.01 (95% CI: 1.51, 6.53), and 2.47 (95% CI: 0.24, 4.70) point improvements in fatigue, energy, and weariness scores, respectively, compared with aMED Q1. Substituting fish for red and processed meat and whole for non-whole grains were associated with more favorable fatigue scores, whereas substituting whole fruit for juice was not.

## **Conclusions**

- 1) Fatigue-related factors mapped into biological, psychological, social, and behavioral factors.
- 2) Researchers in nursing can benefit from using isocaloric substitution methods.
- 3) The aMED was associated with improvements in fatigue. Substituting certain Mediterranean diet featured foods for non-Mediterranean diet foods was related to fatigue improvement.

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## **Acknowledgements**

I am grateful to all the people who have made this work possible. I would like to express my deepest gratitude to my supervisory committee chair, Dr. Oleg Zaslavsky, for his encouragement, mentorship, and constant support of my Ph.D. study and related research. I feel fortunate to be the first Ph.D. student Dr. Oleg Zaslavsky serves as dissertation chair. I truly appreciate his mentorship through my doctoral study's long and arduous journey Dr. Oleg Zaslavsky is indeed the example of a great teacher based on Chinese criteria: immense expertise and virtue. Meanwhile, I am incredibly grateful to my committee members, Dr. Barbara Cochrane, Dr. Kerryn Reding, and Dr. Jerald Herting, for their insightful comments, expertise, and unlimited support for the completion of this dissertation. Sincere gratitude to all my committees for their extraordinary mentorship and visionary comments which have sharpened my thoughts and incited me to deepen research focus and prepare for next academic goals.

Special gratitude to Dr. Lesley Tinker for her nutrition expertise, and Betsy Mau for her support and encouragement throughout this journey. Next, I would like to acknowledge the scholarship support and awards that I received during my doctoral program, including a de Tornyay Healthy Aging predoctoral Scholarship, the Hester McLaws Nursing Dissertation Scholarship award, a de Tornyay Graduate Student Travel Award, Nursing Scholarship Fund & Mitchell Memorial Fund, and School of Nursing Travel Scholarship.

Ultimately, I would like to thank my dear family—Yongde Su (my dad), Houqin Xu (my mom), Min Su (my sister), Chuanhai Zhang (my husband), and Muyan Zhang (my little boy). Their endless love, support, and inspiration are with me in whatever I pursue. As Nightingale said, “Let us never consider ourselves finished nurses ... we must be learning all of our lives”, standing on the shoulders of these wonderful people, I will continuously contribute to advancing nursing science.

## **Chapter 1. Introduction**

### **Content of discussion**

Fatigue, "an overwhelming sustained sense of exhaustion and decreased capacity for physical and mental work at the usual level,"<sup>1</sup> is a common age-related symptom among community-dwelling adults aged 65 years and older.<sup>2</sup> Fatigue affected about 27% to 50% of community-dwelling adults 65 years and older and 75% of adults 85 and older.<sup>3,4</sup> Fatigue was related to an accelerated decline in mobility<sup>5</sup> and cognitive function<sup>6</sup> and risk of hospitalization.<sup>7</sup> The declined function and hospitalization were among the strongest predictors of transitioning from the community to residential care settings or nursing homes.<sup>8,9</sup> Currently, fatigue in community-dwelling older adults has been underrecognized and somewhat poorly managed. Some health professionals considered fatigue as simply tiredness. For example, it has been shown that for close to half (43%) of patients presenting to their general practitioner with fatigue, the final diagnosis will be "tiredness".<sup>10</sup>

Several mechanisms exist to explain fatigue, such as repeated stress reducing the dopamine level then inducing fatigue,<sup>11</sup> the activated immune system causing imbalance of proinflammation and anti-inflammation and finally fatigue,<sup>12</sup> and an imbalance in energy availability and energy expenditure leading to a lack of energy and fatigue.<sup>13,14</sup> Among these mechanisms, an imbalance in energy availability and energy expenditure is the one most relevant to older adults because this mechanism is closely linked to the aging process. For example, the aging-related decline in mitochondrial function can lead to reduced energy production; decreased muscle and heart and lung function increase anaerobic metabolism and lactic acid production; and aging-related low-grade inflammation also leads to fatigue. Particularly, low-grade inflammation has been widely accepted and studied in explaining fatigue in older adults.<sup>12,13</sup> Low-grade inflammation induces a metabolic switch from energy-efficient oxidative phosphorylation to fast-acting but less efficient aerobic glycolytic energy production; increases

reactive oxygen species; and reduces insulin sensitivity.<sup>13,14</sup> These effects result in reduced glucose availability, leading to reduced energy availability. Due to the finite total available energy that can be used and the fact that energy is used to maintain fixed activities. These activities include 1) homeostatic equilibrium, 2) food digestion and body temperature, 3) homeostasis at rest or resting metabolic rate (RMR), and 4) daily activities such as physical and cognitive activities. For older individuals, in the presence of pathology and physiological dysregulation such as comorbidity, self-related health, or pain, require an extra portion of the energy to maintain homeostatic equilibrium; basic activities of daily living and more complex activities may require near maximum energy, with “fatigue” occurring.<sup>13,14</sup>

Nutrition might be especially pertinent to study fatigue because nutrition is closely linked to energy availability and chronic inflammation.<sup>12,15</sup> Even more specifically, among nutrition-related factors, the Mediterranean diet — a way of eating based on the traditional cuisine of Mediterranean countries and typically high in vegetables, fruits, whole grains, fish, beans, nuts and seeds, and olive oil — showed promise from a basic and clinical research standpoint and public interest.<sup>16</sup> A Mediterranean diet has the benefits of protection against inflammation, oxidative stress, modification of hormones, lipid-lowering, and gut microbiota.<sup>16</sup> Compared with other healthy dietary patterns, the Mediterranean diet might be more relevant to studying fatigue in old age as the diet has been ranked No.1 in Best Diets Overall, No.1 in Best Diets for Healthy Eating and No.1 in Easiest Diets to Follow among 40 diets by a panel of health experts. The ranking was the result of comparing short- and long-term weight loss, ease of compliance, safety, and nutrition by health experts, including nutritionists and specialists in different fields.<sup>17</sup>

So far, three studies have been identified that examined the Mediterranean diet and fatigue relationship in people aged 65 years and older.<sup>15,18,19</sup> All these studies, however, were

limited by ad hoc measures of fatigue, which were commonly operationalized as one or two items from the Center for Epidemiologic Studies Depression Scale (CES-D) scales.<sup>15,18,19</sup> An essential step to understand fatigue is to review existing evidence to systematically map what fatigue is, how to measure fatigue, and what factors are related to fatigue for community-dwelling older adults. Beyond the association in examining dietary patterns and fatigue, many studies have started using isocaloric substitution methods (ISM) to look at the nutrition and fatigue relationship from the perspective of substitution rather than association. The study of the Mediterranean diet and fatigue relationship can also benefit from the perspective of substitution because with this perspective; nursing researchers can see that although the physiologic benefits of one food may be similar across individuals, the actual overall impact of that food may have a wide range of effects, depending on each individual's foods limitations, choices, and general lifestyle.

Thus, this dissertation has been organized to understand fatigue and its relationship to the Mediterranean diet among community-dwelling older adults from a unique perspective. Chapter I describes the content to be discussed in the dissertation. Chapter II illustrates fatigue definitions, measures, and factors related to fatigue in community-dwelling older adults. Chapter III provides the utility of ISM approaches in nursing research. We presented a step-by-step example of the ISM framework using both foods and macronutrients as examplers. Chapter IV examines the association between the Mediterranean diet and fatigue and the substitution of fish for red and processed meat, whole grain for refined grain, and whole fruit for fruit juice in relation to fatigue using data from the Women's Health Initiative Long Life Study (WHI LLS).

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**Chapter 2. Fatigue in community-dwelling older adults: A review of definitions, measures, and related factors**

### **Abstract**

Fatigue is a common age-related symptom among community-dwelling adults aged 65 years and older. Yet, a systematic approach has rarely been applied to review definitions, measures, related factors, and consequences of fatigue in this population. A scoping review was conducted in December 2020 to fill the gap, and 36 articles met the inclusion criteria. Definitions of fatigue, albeit diverse, included at least one of the following attributes: an early indicator of disablement, subjective, a lack of energy, multidimensional, impaired daily activities, and temporal. A summary of fatigue measures used in this population was provided, including a brief overview, number of items, reliability, and validity. In general, different measures were used with considerable variability in the content. Additionally, most measures had limited information on test-retest reliability and validity. Fatigue-related factors mapped into biological, psychological, social, and behavioral factors. Fatigue consequences were primarily declines in physical and cognitive functions. (100-150 words)

*Keywords:* fatigue, community-dwelling, older adults, scoping review

## Introduction

Fatigue is one of the most common yet unexplained complaints in primary care settings.<sup>1</sup> Fatigue was reported by 27% to 50% of community-dwelling adults 65 years or older.<sup>2</sup> According to one study from Denmark, the proportion of fatigued older adults increases with age, with about 50% reporting fatigue when they are 70 years old and 75% reporting fatigue when they are 85-year-olds.<sup>3</sup> Fatigue was described as unpleasant,<sup>4,5</sup> debilitating,<sup>6</sup> extremely tired<sup>7,8</sup>, and a loss of control.<sup>9</sup> In addition to the distress, fatigue was also related to an accelerated decline in mobility<sup>10</sup> and cognitive function<sup>11</sup> and a risk of hospitalization.<sup>12</sup> The declined function and hospitalization were among the strongest predictors of transitioning from the community to residential care settings or nursing homes.<sup>13,14</sup> However, fatigue in community-dwelling older adults has been underrecognized and somewhat poorly managed.<sup>15,16</sup> Some considered fatigue as simply tiredness.<sup>17-19</sup> For example, it has been shown that for close to half (43%) of patients presenting to their general practitioner with fatigue, the final diagnosis will be ‘tiredness’.<sup>20</sup>

A definition is essential to truly understand the nature of the concept, and a useful definition guides intervention strategies.<sup>21</sup> However, there is still a lack of clarity in definitions for fatigue. For 230 years, there has been a lack of consensus in fatigue definition and a blurred boundary between fatigue and related concepts.<sup>22</sup> By reviewing fatigue definitions from multiple disciplines, we might facilitate fatigue management via strengthening interprofessional teamwork. Currently, community-dwelling older adults who comprise a large portion of overall older adults (more than 95%)<sup>23</sup> suffer from heavy symptom burdens. As reported by a nationally representative study, there was a high burden of symptoms among community-dwelling older adults in the United States; approximately half of older adults reported two or more symptoms, and more than a quarter reported three or more symptoms, with pain and fatigue as the most

common co-occurring symptoms.<sup>24</sup> Thus, to better manage fatigue in community-dwelling older adults, it is critical to review fatigue definitions among community-dwelling older adults.

While a conceptual definition is critical, clinicians and nurses should use an operational definition or measure/instrument to diagnose or monitor fatigue. Ideally, the tool should be reliable, valid (e.g., able to distinguish who are fatigued from those who are not), and easy to implement. Currently, in the nursing field, the criteria to diagnose/assess fatigue are not based on a measure/instrument but instead on the conceptual definition by the North American Nursing Diagnosis Association (NANDA), which defines fatigue as “an overwhelming sustained sense of exhaustion and decreased capacity for physical and mental work at the usual level” (p. 242).<sup>25</sup> For clinicians, guidelines state that fatigue is a clinical diagnosis that can be made only when other disease processes are excluded.<sup>26</sup> Across countries, researchers have reported a lack of formal guidelines on how to approach patients presenting with fatigue.<sup>27–29</sup>

It is critical to accurately assess fatigue in community-dwelling older adults and identify the factors that contribute to fatigue in this population. Fatigue in this population probably results from complex, poorly understood interactions between biological (mitochondria, telomeres, and low-grade inflammation), physiological (musculoskeletal system, cardiovascular and pulmonary system, and the neurological system)<sup>3</sup>, psychosocial (repeated stress, reduced motivation), and behavioral (impaired sleep and daily activities) phenomena.<sup>30,31</sup> Although researchers have conducted systematic reviews about factors contributing to fatigue in people with specific diseases (e.g., stroke patients,<sup>32</sup> osteoarthritis patients,<sup>33</sup> cancer patients,<sup>34</sup> or patients with COPD<sup>35</sup>), none have done a systematic search of fatigue-related factors in community-dwelling older adults who usually suffer from multiple chronic conditions. An essential step toward better management of fatigue in community-dwelling older adults is to review existing evidence to

systematically map what is known from the literature about fatigue definitions, measures, and related factors in community-dwelling older adults and identify any existing gaps. We formulated three research questions: 1) what fatigue definitions have been used in community-dwelling older adults, 2) what measures have been used to measure fatigue in community-dwelling older adults, and 3) what factors have been reported as related to fatigue in community-dwelling older adults?

## **Methods**

### **Framework**

This scoping review followed guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR),<sup>36</sup> which was built upon prior scoping review frameworks of the Joanna Briggs Institute (JBI)<sup>37</sup> and Arksey and O'Malley.<sup>38</sup> The PRISMA-ScR framework deleted five items (e.g., risk of bias across studies, risk of bias within studies, further analysis) from the original PRISMA checklist, and it had the following main steps: 1) indicate whether a protocol and registration exist; 2) eligibility criteria; 3) information sources & search; 4) selection of sources of evidence; 5) charting data from the selected studies; and 6) synthesis of results.<sup>36</sup>

### **Stage 1: Protocol and registration**

We did not develop a protocol before drafting this scoping review paper.

### **Stage 2: Eligibility criteria**

All peer-reviewed original articles retrieved from the following four databases were considered eligible for further review. Inclusion criteria were as follows: 1) human subject  $\geq 65$  years old; 2) community-dwelling (the descriptions we looked for were “community-dwelling older adults”, “recruited directly from a community-setting”, or “a sample that represents community-dwelling older adults”); 3) fatigue is the main focus of the paper; the paper has to

have a description of what fatigue is OR has to have measured fatigue; 4) full-text available in English.

### **Stage 3: Information sources & Search**

PubMed, CINAHL, PsycINFO, and Social Work Abstracts were searched for relevant studies. YS and an experienced librarian who also has expertise in health science performed the literature search. The keywords or combinations of Medical Subject Headings (MESH) were modified to optimize search strategies in each database. A literature search using keywords of “fatigue” AND “community-dwelling” AND (“older adults” or senior or elder or geriatric) was conducted in December 2020 without setting a time frame limitation. The detailed search terms are presented in **Supplementary Table 2.1**.

### **Stage 4: Selection of sources of evidence**

Zotero software<sup>39</sup> was used to check for duplicates, and Rayyan was used to review.<sup>40</sup> YS and RY independently accessed Rayyan and independently examined the titles and abstracts to assess their relevance for the review. Next, YS and RY independently retrieved and reviewed full texts. Any disagreements on study selection were resolved by consensus and discussion with other authors if needed. The workflow is shown via the PRISMA-ScR guideline (**Figure 2.1**).

### **Stage 5: Charting the Data**

We generated a data-charting form to guide the data abstraction process and display a summary of these study features: author, publication year, field (department), conceptual terms (what the authors called "fatigue" in the publication), detailed definition, measure, related factors, and consequences. The table was created in such a format that content could be summarized meaningfully (**Table 2.1**).

### **Stage 6: Synthesis of results**

We reported results in the order of 1) definitions, 2) measures, and 3) related factors of fatigue and consequences. 1) The definition was reported in the form of attributes, namely the real characteristics or core qualities of the concept that make it possible to distinguish between the defined attributes of a concept and irrelevant points.<sup>21</sup> Fatigue attributes were measured as frequent words or expressions used to describe the experience of fatigue from the included studies (**Table 2.1**).<sup>21</sup> 2) Measures included a brief overview, the number of items, reliability, and validity. Reliability mainly included reliability (e.g., test-retest reliability), internal consistency, and other components.<sup>41</sup> Validity mainly included construct validity (e.g., structural, hypothesis testing), criterion validity (e.g., predictive validity, concurrent validity), and other components.<sup>41</sup> The reliability and validity were identified by tracing back to the original papers that developed the measures and other documents that also checked the properties of that measure in different samples (**Table 2.2**). 3) Related factors were what contributed to the occurrence of fatigue. Consequences were what followed the event of fatigue. Related factors and consequences were determined by study aims. Specifically, related factors were extracted if the study aimed to identify factors that can predict the level of fatigue, and consequences were extracted if the study aimed to examine what elements can be indicated by fatigue (**Figure 2.2**).

## **Results**

### **Study Selection and Characteristics**

The search resulted in 199 articles in PubMed, 172 articles in CINAHL, 59 articles in PsycINFO, and 90 articles in Scopus. After duplication checks, a total number of 338 were retrieved. Titles and abstracts were initially examined for relevancy, which resulted in 72 articles. Subsequent assessment of full article eligibility criteria led to a final list of 36 articles (**Figure 2.1**). All the articles meeting the analysis criteria were published between the years 2002 and 2020. Studies were conducted around the world, including the USA (n=16), Europe (n=9),

Asia (n=6), and other places (n=5). Only eight articles were from the nursing field (based on the first author's departments), 18 from medicine or public health departments, four from physical therapy, and the rest from psychology (n=1), gerontology (n=1), kinesiology (n=2), lifelong health and aging (n=1), and social work (n=1). The populations included community-dwelling older adults in general (n=30); those with diabetes (n=1), heart failure (n=1), chronic anemia (n=1), osteoarthritis (n=1), octogenarians and centenarians (n=1), and not mentioned (n=1). Twenty-five studies used cross-sectional designs, nine were longitudinal studies, and two examined the psychometric properties of fatigue instruments. The conceptual terms being used included fatigue, self-perceived fatigue, symptomatic fatigue, subjective fatigue, task-specific fatigue, daytime fatigue, chronic fatigue, perceived global fatigue, mobility-related fatigue, fatigability, and general fatigue.

### **Prevalence**

It was widely accepted that fatigue in community-dwelling older adults was a common complaint.<sup>17,18,42-50</sup> One study reported that fatigue was prevalent among older primary care patients, with 70% reporting one or more fatigue qualities (e.g., physical, mental) and 43% reporting feeling tired most of the time.<sup>45</sup>

### **Definition**

The most commonly accepted definition of fatigue was a subjective sensation of weakness, lack of energy, and tiredness.<sup>42,51-54</sup> The literature also showed a wide variety of conceptual understandings of fatigue. For example, although most studies described fatigue as a multidimensional symptom and a lack of energy, four studies defined fatigue as simply tired<sup>17,19</sup> or persistently tired or tired most of the time.<sup>18,55</sup> One study considered fatigue as one construct of mental health and defined it as a lack of interest or decline in daily activities and feelings of

reduced energy.<sup>56</sup> The attributes of fatigue as a concept included six aspects: an early indicator of disablement, subjective, lack of energy, multidimensional, impaired daily activities (behaviors), and temporal.

**An early indicator of disablement.** Fatigue was reported to be a strong indicator of rapid aging,<sup>57</sup> of aging-related declines in health and functional abilities,<sup>58</sup> and as a self-reported indicator of early frailty.<sup>46,57</sup> Fatigue was also an indicator of ill-health among older populations worldwide.<sup>17</sup> More importantly, fatigue was reported as an early indicator of disablement or disability in older adults across countries.<sup>59,60, 61,57</sup> An early indicator of disablement means that a fatigued individual may maintain his desired or usual performance and function, but the required energy is near maximum capacity.<sup>31</sup>

**Subjective.** Fatigue was an abstract feeling that could be perceived but was hard to measure. From the included definitions, fatigue has been described as a subjective feeling.<sup>5,19,43,48,53,62–64</sup> The terms used to describe fatigue like self-perceived fatigue, symptomatic fatigue, subjective fatigue, perceived global fatigue, and subjective vitality indicated this property.

**Lack of energy.** Energy referred to the capacity for doing work. A lack of energy could be defined as an inability to perform specific tasks. From the included articles, the most commonly reported characteristic of fatigue was a lack of energy.<sup>42,47,48,50–53,56,57,62,63,65,66</sup> Most studies used the exact words “lack of energy,” “depleted energy,” or a misbalance of energy such as “a mismatch between task-related energy requirements and available energy resources”<sup>50</sup> or “a decrease in the production of energy”.<sup>57</sup> Others used words like “inability” such as inability to complete normal daily activities<sup>65</sup> or inability to cope with an increase in the utilization of

energy, which presents as general fatigue in older people when they perform even mild daily activities”.<sup>57</sup>

**Multidimensional.** Most researchers indicated fatigue was a multidimensional symptom. Specifically, two studies defined fatigue as a reduction in performance and efficiency and a lack of interest in working, encompassing sensations that involve the whole body.<sup>4,5</sup> Many studies acknowledged that fatigue involved physical and mental dimensions and defined fatigue as physical and mental weariness resulting from exertion.<sup>5,44,45,47,51,62,67</sup> *Physical fatigue* was generally experienced as a severe state of tiredness,<sup>5,17,53,62</sup> strain, weakness, sleepiness, and low strength.<sup>45</sup> *Mental fatigue* was experienced as a lack of motivation,<sup>4,45</sup> unpleasant symptoms,<sup>4,5</sup> mood, and enjoyment.<sup>6</sup> Physical fatigue was more common than mental fatigue among older adults.<sup>45</sup>

**Impaired daily activities (behaviors).** Most studies stated that fatigue interfered with daily or routine activities.<sup>19,43,44,57,63–65,67</sup> Specifically, it was reported that fatigue interrupted usual and desired actions,<sup>44,65</sup> mild daily activities,<sup>57</sup> or even initiating activities.<sup>19</sup> Of note, the term fatigability was used continuously to replace fatigue when talking about the inability to continue activity at the same intensity.<sup>67</sup> Fatigability was a new construct that measured self-reported fatigue in performing a standard dosage of exercise/activity,<sup>62</sup> which allowed meaningful comparisons across subjects and between studies.<sup>68</sup>

**Temporal.** Temporal included the timing of fatigue occurrence, the frequency, duration of fatigue, pattern, and the change in patterns.<sup>69</sup> Although many authors missed this trait, it was indicated by a few authors.<sup>18,47,54,55,70</sup> Fatigue temporal trait was reported as “tired most of the time”,<sup>55</sup> “persistent general tiredness”,<sup>18</sup> “sustained exhaustion and a decreased capacity”.<sup>47</sup> One study slightly indicated the change in patterns: fatigue was not relieved by rest.<sup>47</sup> Specifically,

chronic fatigue was defined as exhaustion lasting six months or longer<sup>54</sup>, and fatigability was defined as perceptions of fatigue in the context of a fixed intensity and duration.<sup>70</sup>

## Measures

Thirty out of 36 studies used only one fatigue measure, and four studies adopted two measures.<sup>44,46,58,59</sup> Six studies used an investigator-self developed one-item measure such as general fatigue level.<sup>18,49,55,58,62,65</sup> The most widely adopted instrument was the SF-36 vitality subscale (n=5),<sup>71</sup> which assessed overall body energy.<sup>71</sup> Other instruments or subscales of these instruments were also identified, including the Fatigue Severity Scale (FSS) (n=2),<sup>72</sup> Mobility-Tiredness (Mob-T) Scale (n=5),<sup>73</sup> Revised Piper Fatigue Scale (n=1),<sup>74</sup> Brief Fatigue Inventory (BFI) (n=1),<sup>75</sup> Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F) (n=2),<sup>76</sup> Visual Analogue Scale for Fatigue (VAS-F) (n=2),<sup>77</sup> Multidimensional Fatigue Inventory (MFI) (n=3),<sup>78</sup> and Pittsburgh Fatigability Scale (PFS) (n=2).<sup>79</sup> While the majority were self-reported fatigue levels, two measures were objective or performance-based, measuring the decrease of the maximum velocity of performance or measuring balance control before and after fatiguing the ankle and knee.<sup>9,67</sup> The measured content covered various aspects such as energy level, limited behaviors, frequency of symptoms, etc. The number of items ranged between one and 32, with most of the measures having less than ten items. Almost half of the 25 measures (n=12) were author self-created questions or selected items from existing measures. Only four out of 25 measures had test-retest reliability (i.e., FACIT-F,<sup>76,80</sup> FSS,<sup>72</sup> PFS,<sup>79</sup> & Checklist Individual Strength<sup>81</sup>), and the rest only reported internal consistency or did not report. Among the 25 measures, 14 reported criterion or criterion related validity, four reported construct validity, and only three reported both (i.e., SF-36 Vitality,<sup>71</sup> Mob-T,<sup>73</sup> & BFI<sup>6</sup>). More details can be found in **Table 2.2**.

## Fatigue-related Factors

All identified related factors from the final list of articles can be categorized into biological (i.e., inflammation,<sup>46,50,66</sup> energetic,<sup>62</sup> pain,<sup>17</sup> adiposity,<sup>66</sup> comorbidity,<sup>4,52</sup> self-related health,<sup>4</sup> low hemoglobin,<sup>53</sup> tooth loss<sup>60</sup>, heart failure<sup>82</sup>), behavioral levels (i.e., physical activity,<sup>4,56,62,66</sup> sleep duration and quality,<sup>42,48,51,52,83</sup> malnutrition<sup>44</sup>), psychological (i.e., depressive symptoms,<sup>52,58,66</sup> stress<sup>56</sup>), and social levels (i.e., social support<sup>47,56</sup>). See **Figure 2.2**.

Biologically, four studies indicated that fatigue might be related to inflammatory factors. One study examined the relationship between C-reactive protein (CRP) and fatigue in older women and found CRP was a significant independent predictor of fatigue, explaining 6.6% of the variance, as were depression (6.3%), physical activity (5.8%), and %Fat (3.9%).<sup>66</sup> In another study, body mass index (BMI), CRP, and interleukin 6 (IL-6) were each associated with fatigability scores after adjusting for a range of potential confounders.<sup>70</sup> Another study found a significant association between white cell count<sup>46</sup> and fatigue. Based on the findings, the authors hypothesized that any combination of factors known to promote inflammatory risks might relate to fatigue,<sup>46</sup> and once an individual had symptoms of fatigue, these symptoms themselves were likely to promote further inflammatory activation through several pathways, such as increased life stress, depression, and fatigue development.<sup>46</sup> Finally, other researchers found people in the high fatigability cluster had significantly higher IL-6 levels than those in the low fatigability cluster.<sup>50</sup> Except for inflammatory factors, other biological factors involved metabolic and energetic requirements. Researchers investigated the correlation between perceived fatigue, metabolic measures, and energy cost (O<sub>2</sub>cost measured in ml O<sub>2</sub>/kg/m) of walking in older women.<sup>62</sup> They found that perceived fatigability was not related to metabolic measures but to greater O<sub>2</sub>cost ( $r = 0.579, p < 0.01$ ). The authors offered a plausible explanation that greater

fatigue levels were experienced when the body required a greater proportion of energy to perform daily tasks.<sup>62</sup>

Behaviorally, the most commonly reported related factors of fatigue were sleep-related factors, physical activity, and malnutrition. Regarding sleep, both short and long sleep duration<sup>42,51</sup> and sleep quality<sup>48,52</sup> were associated with fatigue. Specifically, researchers found that self-reported short sleep duration (<6 hours) and waking up too early in the morning were significantly associated with higher fatigue after controlling for BMI, poorer self-reported health status, high depressive symptoms, prevalent cardiovascular disease, etc.<sup>42</sup> Another study among older adults with diabetes found that poor sleep quality (B = 0.762, 95% CI [0.095, 1.428]) was most strongly associated with fatigue, followed by comorbidity (B = 0.752, 95% CI [0.096, 1.408]), and psychological variables, including depression (B = 0.166, 95% CI [0.066, 0.265]), difficulty with meal planning (B = 0.291, 95% CI [0.091, 0.490]) and satisfaction with diet (B = -0.133, 95% CI [-0.219, -0.047]).<sup>52</sup> Finally, older adults with osteoarthritis reported that on awakening from a night of poor quality sleep, fatigue intensity was heightened, but the effect was not sustained throughout the day, suggesting the morning may be an optimal time for symptom interventions.<sup>48</sup> Behavioral variables such as physical activity and nutrition-related variables like malnutrition<sup>44</sup> were also related to fatigue. Researchers reported that physical activity was consistently related to less fatigue,<sup>4,56,62,66</sup> and physical activity related to muscle fatigue and self-perceived fatigue.<sup>4</sup>

Psychological factors included depressive symptoms and stress. Depressive symptoms were a prominent contributor to fatigue.<sup>52,58,66</sup> One study showed that depressive symptoms were more related to general fatigue than mobility-related fatigue.<sup>58</sup> Another study showed self-

perceived fatigue was more related to depressive symptoms than muscle fatigue.<sup>4</sup> Another study found social support and physical activity mediated the relationship between stress and fatigue.<sup>56</sup>

Socially, one study examined the relationship between functional and psychological factors and fatigue among octogenarians and centenarians.<sup>47</sup> The study showed functional capacity variables and social support were significant predictors of fatigue among these oldest-old adults.

### **Consequences**

The most commonly reported consequence of fatigue was functional decline, mainly physical<sup>5,18,19,59,64,84</sup> and cognitive functioning.<sup>19</sup> Other consequences included control of balance<sup>64,84</sup> and functional mobility measured by the Timed Up and Go (TUG) test.<sup>64</sup> Researchers from one cross-sectional study stated that the negative relationship between fatigue and physical functioning remained significant even after accounting for depression.<sup>44</sup> A longitudinal study showed an independent association between fatigue and cognitive-related functioning (e.g., speed of processing, memory, reasoning, everyday problem-solving) remained significant even after controlling depression and grip strength.<sup>19</sup> Finally, one study reported that older adults' medical conditions affected their physical and other functioning through the effect of fatigue.<sup>85</sup> To sum up, it seems fatigue is closely related to worse functioning, especially physical functioning.

### **Discussion**

This review is the first to summarize fatigue definitions, measures, and associated factors and consequences in community-dwelling older adults. As a scoping review, our findings were based on published literature. In this work, we aimed to present the definition, measure, and associated factors of fatigue in community-dwelling older adults. We identified the following attributes of fatigue in this population: an early indicator of disablement, subjective, a lack of

energy, multidimensional, impaired daily activities, and temporal. We presented fatigue measures used in this population, including a summary of the content, number of items, reliability, and validity. Various measures are being used and the content varied significantly. Almost half of the measures were author self-created questions or selected items from existing tools. Many measures lack information on test-retest reliability, construct validity, and various types of criterion validity. Finally, we reported fatigue-related factors and consequences. Fatigue-related factors mapped into biological, psychological, social, and behavioral factors. The consequence was primarily declined physical and cognitive functions.

Attributes underlie a concept. The attributes of fatigue in community-dwelling older adults are different from those previously published in the general population, children with chronic conditions, and long-haul drivers. For example, “an early indicator of disablement” and “impaired daily activities (behaviors)” are unique and only reported in community-dwelling older adults. “Impacted by developmental stage” is unique attribute of fatigue in children with chronic conditions.<sup>86</sup> Decreased eye movement, impaired alertness, lapsed attention, sensory disturbance, and impairments in information processing and judgment are unique attributes of fatigue from long-haul drivers.<sup>87</sup> Researchers and clinicians should be aware that fatigue has different attributes in different populations, and the attributes of fatigue in community-dwelling older adults should be used when working with this population.

A variety of measures are being used to measure fatigue, which reflects the nature of fatigue being heterogeneous and multifaceted and serving different purposes (screening, diagnosis, etc.) for these measures to be used. Although it is challenging to compare these measures, it is helpful to have a thorough evaluation of these measures to select the real high-quality fatigue measures. In the current scoping review, we evaluated some components of

reliability and validity but we suggest future researchers conduct a detailed evaluation based on COSMIN (Consensus-based Standards for selecting health Measurement Instruments) framework<sup>88</sup> or a modified taxonomy provided by Polit and Yang,<sup>89</sup> which assessed reliability (including measurement error), validity (other types of validity such as content validity), change, and responsiveness. Almost half of the measures were a single item or selected items from fatigue measures lacking information on their reliability and validity. Only four out of 25 measures had test-retest reliability, and most studies had insufficient information concerning their validity. Thus, more studies are required to assess the test-retest reliability and validity aspects of the measures. Noteworthy, measures with good test-retest reliability are essential to provide reliable and continuous monitoring of fatigue development.

Fatigue-related factors in community-dwelling older adults covered biopsychosocial and behavioral aspects, which reflected fatigue's complex pathways/pathophysiology. Specifically, each related factor seemed to contribute to fatigue independently. For example, when body mass index (BMI), poor self-reported health status, high depressive symptoms, prevalent cardiovascular disease, and sleep variables were all in the regression model, each related factor was still significantly associated with higher fatigue.<sup>42</sup> Each factor seems to affect fatigue in a different and unique pathway. For example, depressive symptoms might affect fatigue through an emotional path.<sup>4,58</sup> Bodily factors such as adiposity or pain and muscular factors might affect fatigue through the body.<sup>45</sup> Sleep quality might be associated with fatigue through the temporal route.<sup>48</sup> Metabolic and energetic related factors might affect fatigue through O<sub>2</sub>cost.<sup>62</sup> A next step might be quantitatively synthesizing the relationship between each related factor and fatigue by calculating effect sizes to facilitate the comparison among these factors and identify the most

relevant related factors. One approach to achieve that might be relaxing the criteria of older adults from 65 to 60 to increase the sample sizes.

Regarding consequences, fatigue was significantly related to a declined physical and cognitive functioning. Based on previous studies, subjects with lower functional performance were five times more likely to develop functional dependence in the future than those without such impairments.<sup>19</sup> Daily living dependencies of three or more activities (summary odds ratio [OR] = 3.25, 95% confidence interval [CI] = 2.56–4.09) and cognitive impairment were among the strongest predictors of nursing home admission (OR = 2.54, 95% CI = 1.44–4.51).<sup>13</sup> Similarly, a recent study of community-dwelling U.S. older adults from 2011 to 2018 showed having functional and cognitive limitations was associated with an increased risk of transitioning to residential care settings or nursing homes from the community.<sup>14</sup> Thus, early and accurate recognition of fatigue might provide an opportunity to delay consequences such as declined functioning, which might help maintain community residency.

Our findings should be interpreted with limitations. First, none of the 36 studies used a qualitative design with interviews of stakeholders' (older adults themselves') opinions about what fatigue is; thus, the literature reflected the current usage in the literature or researchers' understanding of fatigue. Stakeholders' responses, which reflected their own experiences regarding fatigue, may differ from health professionals' or researchers'. For example, nurses are less involved with the patient's daily life, and their views of fatigue might be limited to a functional and professional domain.<sup>90,91</sup> The absence of stakeholders' opinions reflects a lack of qualitative studies in community-dwelling adults older than 65 years. Future researchers may consider more qualitative studies to investigate how community-dwelling older adults themselves view fatigue and its effect in their lives. Another limitation is that we specifically

defined older adults as adults 65 years and older, so the definitions of fatigue in some developing countries where older adults are defined as adults older than 60 or 55 or without a specific age definition are not represented in the current study. Although this limitation excluded a small percentage of relevant sources, a decision was made to facilitate replicability and promote transparency and efficiency. Finally, because the designs of many studies were cross-sectional, some variables analyzed as "related factors" could actually have been consequences. Such taxonomy of related factors and consequences was based on the study aims to facilitate reporting each study's findings.

### **Conclusion**

This scoping review identified the following attributes of fatigue in community-dwelling older adults: an early indicator of disablement, subjective, a lack of energy, multidimensional, impaired daily activities, and temporal. We summarized fatigue measures and provided a brief summary of the content, number of items, reliability, and validity. Different measures were used and content varied considerably. Most measures lacked information on their test-retest reliability and validity. Fatigue-related factors mapped into biological, psychological, social, and behavioral factors. Fatigue consequences were primarily declined physical and cognitive function. Accurate recognition and effective management of fatigue may delay outcomes such as impaired functioning, which might help maintain independence. Future researchers should be aware of the attributes of fatigue in community-dwelling older adults and apply reliable and valid measures that are suitable to assess fatigue in this population. Meanwhile, more efforts should be diverted to check the reliability and validity of the existing measures. Finally, to better understand the pathways leading to fatigue, we call researchers to quantitatively synthesize the effect of all related factors on fatigue by calculating their effect sizes to identify the most relevant elements.

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**Table 2.1** Attributes, Measurements, Related Factors, and Consequences of Fatigue in Community-Dwelling Older Adults: Findings from the Literature (n=36)

Author, Year, & Field	Term	Definition (attributes highlighted)	Measure(s)	Related factors	Consequences
Barak, 2020, Psychological Medicine [65]	Fatigue	The interRAI defines fatigue as: “ <b>Inability</b> to complete <b>normal</b> daily <b>activities</b> .”	Self-created fatigue severity measurement	Depression explained only 0.2% of fatigue.	
Pérez et al., 2019, Medicine [63]	Perceived global fatigue	Perceived global fatigue refers to a subjective self-report of global <b>tiredness</b> and <b>lack of energy</b> , which leads to decreased physiological reserve, <b>functional decline</b> and <b>disability</b> .	PFS		Higher PFS physical scores were inversely associated with the Short Physical Performance Battery
Cooper et al., 2019, Lifelong Health and Ageing [70]	Fatigability	<b>Perceptions</b> of fatigue in the context of specific standard activities of <b>a fixed intensity and duration</b>	PFS	BMI, CRP and IL-6 were each associated with PFS scores.	
Kim, 2019, Nursing [52]	Fatigue	It often refers to tiredness, lack of <b>energy</b> , or weariness.	FSS	Comorbidity and psychological factors (depression, sleep quality, and diet-related psychological characteristics) were significant predictors of fatigue.	
Liu et al. 2019, Nursing [57]	General fatigue	Many older people experience general fatigue. It refers to a decrease in the <b>production of energy</b> or an <b>inability</b> to cope with an increase in the utilization <b>of energy</b> , which <b>presents as general fatigue in older people when they perform even mild daily activities</b> .	The Chinese MFI		This is a protocol study
Whibley et al., 2019, Medicine [48]	Fatigue	Fatigue is a <b>subjective</b> experience, described as a feeling of overwhelming <b>tiredness</b> , <b>exhaustion</b> , and <b>lack of energy</b> , <b>commonly</b> experienced by older adults with osteoarthritis	Questions from CESD	On awakening from a night of poor-quality sleep, pain and fatigue intensity were heightened among older adults with osteoarthritis.	
Broström et al., 2018, Nursing [51]	Fatigue	Fatigue is defined as <b>mental</b> and <b>physical</b> components and overlaps with other constructs,	SF-36 vitality subscale	Too short or too long sleep duration (only in	

		such as lack of <b>energy</b> , tiredness, and lack of strength.		older men) related to more fatigue.	
Romine, 2017, Medicine [17]	Task-specific fatigue	Fatigue is a common condition contributing to <b>disability</b> among older patients. Fatigue is an important <b>indicator of health</b> among older populations worldwide.	Mob-T	Pain was the only attribute consistently predictive of fatigue status.	Self-reported chair rise fatigue and walking fatigue were associated with task performance
Shuman-Paretsky et al., 2017, Medicine [43]	Cognitive Fatigue	The <b>executive failure to maintain and optimize performance over</b> acute but sustained cognitive effort	The State-Trait Inventory for Cognitive Fatigue (STI-CF)		This is a scale development
Barbosa et al., 2016, Physical therapy [62]	Perceived fatigue	Perceived fatigue, defined as <b>lack</b> of subjective <b>physical and/or mental energy</b> , self-report their overall feelings of <b>tiredness</b> irrespective of the specific context. Fatigability is a new construct that describes how fatigued an individual gets in relation to <b>defined activities</b>	current level of tiredness immediately after the 6-minute walk test (6MWT).	The severity of perceived fatigability was significantly correlated with greater O2cost, physical activity, walking distance and severity of performance fatigability	
Lindemann, 2016, Medicine [67]	Fatigability	Fatigue is defined as <b>physical and/or mental</b> weariness resulting from exertion. Fatigability describes the <b>inability to continue activity</b> at the same intensity <b>resulting in deterioration of performance.</b>	Performance based test		This is a test protocol
Christie et al., 2016, Kinesiology [83]	Self-reported fatigue	A common complaint in older individuals	Patient-Reported Outcomes Measurement Information System (PROMIS)	An inverse relationship was found between sleep quality and fatigue in the older	
Soares et al., 2015, Physical Therapy [5]	Self-perceived fatigue	Self-perceived fatigue is characterized as a <b>subjective</b> , conscious, and unpleasant symptom that involves the <b>whole body and</b> may be influenced by intrinsic and extrinsic factors. A conscious report of <b>tiredness</b> is the most relevant information for fatigue evaluation.	Self-reports based on the CESD		Fatigue related to poor lower extremity function, usual gait speed, activity limitation, and participation restriction in older adults
Mänty et al., 2014, Public Health [58]	General fatigue	Fatigue is considered an important <b>indicator</b> of aging-related <b>declines</b> in health and functional <b>abilities.</b>	Mob-T	Depressive symptom was a strong predictor of mental fatigue	

Lin et al., 2014, Nursing [50]	Fatigability	Mismatch between task-related <b>energy</b> requirements and available <b>energy</b> resources.... Fatigue is one of the most <b>common somatic symptoms</b> reported by older adults.	The change between self-reported acute fatigue before and after the series of cognitive tests		Participants with high fatigability had significantly higher interleukin 6 (IL-6) response levels than the low fatigability group
Shuman-Paretsky et al., 2014, Psychology [6]	Fatigue	<b>Subjective</b> fatigue has been proposed to be a physiologic <b>warning signal of impending disease events.</b>	The BFI		This is a tool development study
Lin, 2013, Nursing [19]	Subjective fatigue	The <b>feeling</b> of being <b>tired</b> or having <b>difficulty in initiating activities</b>	SF-36 vitality subscale		There is an independent causal relationship between subjective fatigue and decline rate in cognitive and functional abilities beyond the influence of depression, grip strength, etc.
Baskurt et al., 2012, Health Science [64]	Self-perceived fatigue	Fatigue is a <b>subjective</b> feeling of <b>low vitality</b> that <b>disrupts daily functioning</b>	Turkish version of checklist individual strength (CIS-T)		Self-perceived fatigue was related with lower extremity function, usual gait speed and activity limitation and participation restriction.
Tennant, 2012, Nursing [44]	Symptomatic fatigue	Fatigue is such a frequent complaint among the elderly.... Symptomatic fatigue is a <b>subjective</b> lack of <b>physical</b> and/or <b>mental energy</b> that is perceived by the individual to interfere with <b>usual and desired activities</b>	FSS & FACIT-F	Fatigue was associated with a greater incidence of risk for malnutrition.	Decreased physical function performance, lower morale, and reduced physical composite scores remained significant even after accounting for depression scores.
Cho, 2012, Public Health, gerontology [47]	Fatigue	Fatigue is a common and frequently observed complaint among older adults. Fatigue is defined as 'a <b>subjective</b> state of overwhelming, <b>sustained exhaustion</b> and a <b>decreased capacity for physical and mental work</b> that is not relieved by rest'	MFI	Self-rated health and instrumental activities of daily living, both positive and negative affect, and social support were significant predictors of fatigue	

Avlund et al., 2012, Medicine [46]	Fatigue	Fatigue is a common <b>complaint</b> among older adults and one of the most frequent reasons for encounter in general practice.	1) General fatigue, a question from the SF-12 questionnaire. 2) Mobility-related fatigue, Avlund Mob-T Scale	White blood cell counts, neutrophils, and lymphocytes were associated with fatigue	
Schnelle, 2012, Medicine and Public Health [49]	Fatigability	Fatigue is a <b>common</b> problem in people with chronic disease and an important component of definitions of frailty. The term fatigability severity is defined as <b>differences</b> between people in the <b>activity level</b> that leads to greater fatigability.	Directly asking participants to report change in energy after a standardized 10-minute walk at a self-selected pace.		This is a test of validity between two fatigability scales. Perceived and performance fatigability were significantly correlated
Chou, 2012, Social Work [54]	Chronic fatigue	" <b>Self-reported</b> , persistent, and disabling <b>tiredness, weakness, or exhaustion lasting 6 months or longer</b> ". more common among women.	In the fatigue section of the revised clinical interview schedule,		Chronic fatigue was significantly related to affective disorders of depression, mixed anxiety
Silva, 2011, Physical Therapy [4]	Self-perceived fatigue	"A reduction in the performance, a loss of <b>efficiency</b> and/or a lack of <b>interest</b> in working. The self-perceived fatigue can be understood as a conscious and unpleasant symptom, encompassing <b>sensations that involve the whole body.</b> "	VAS-F	Predictors included a large number of comorbidities, worse depression status, poorer health perception, lower levels of physical activity, poorer physical functioning and lower peak torque. Self-perceived health and level of physical activity were the factors that most explained the variation in self-perceived fatigue.	
Kwag, 2011, Gerontology, aging [56]	Fatigue	One construct of mental health. Lack of interest with <b>declines of daily activities</b> and feelings of <b>reduced energy</b> .	Fatigue Scale was part of the Eight State Questionnaire (8SQ).	Social support and physical activity mediated the relationships between stress and mental health (e.g., fatigue, loneliness, and depression)	

Avlund et al., 2011, Medicine [60]	Fatigue	Fatigue in daily activities is an <b>indicator of early-stage disability</b> in older adults	Mob-T		Tooth loss was correlated with fatigue
Moreh et al., 2010, Medicine [18]	Fatigue	Fatigue is common among the elderly. Fatigue is a sense of <b>persistent general tiredness</b> "	"Do you feel generally tired?"		Fatigue among the elderly people, including the oldest old, had a significant negative impact on health status, function, and mortality.
Hardy & Studenski 2010, Medicine [45]	Fatigue	Fatigue was very common among older primary care patients. <b>Physical</b> fatigue qualities were <b>more common than mental qualities</b> . The most frequent types are <b>mental</b> fatigue, which may be subdivided into <b>emotional and cognitive, and physical</b> fatigue, which may be subdivided into sleepiness, low <b>strength</b> , and <b>energy loss</b> .	"Have you felt tired most of the time in the past month?"		Among older primary care patients, with 70% reporting one or more fatigue qualities and 43% reporting feeling tired most of the time, and was associated with worse health and functional status.
Valentine, 2009, Kinesiology and Community Health [66]	Fatigue	Fatigue is a serious health concern. It is a <b>perception</b> and a low in <b>energy</b>	Two items taken from the CHIPS	In women, fatigue was independently explained by C-reactive protein (6.6%), depression (6.3%), physical activity (5.8%), and adiposity (3.9%); however, in men, only depression explained variance in fatigue (12.0%).	

Goldman, 2008, Neurology [42]	Daytime Fatigue	"Weariness, weakness, tiredness, and depleted <b>energy</b> " is a <b>multidimensional</b> , nonspecific syndrome that occurs commonly in older adults..... Fatigue is often confused with daytime sleepiness. Although fatigue and daytime sleepiness are separate constructs, measures used to define fatigue and sleepiness may often overlap. Questionnaires to determine fatigue do not consistently evaluate sleepiness as a component of fatigue.	Subscale from the revised Piper Fatigue Scale	Self-reported short sleep duration, and waking up too early were significantly associated with fatigue	
Avlund et al., 2008, Medicine, [59]	Fatigue	Fatigue in daily activities is an <b>indicator of an early stage of disablement</b> in older adults.	1) vitality from the SF-12 questionnaire. 2) Mob-T		Subsequent physical functioning (such as moving a table, pushing a vacuum cleaner or bicycling? 2) climbing several flights of stairs) and use of health services (e.g., health care utilization included contacts with the general practitioners: consultations, telephone advice, and home visits)
Ha'gglund et al., 2008, Nursing, [80]	Fatigue	Troublesome symptoms for patients with heart failure	Multidimensional Fatigue Inventory-20 (MFI-20)	People with heart failure symptoms have more fatigue	
Hardy & Studenski, 2008, Medicine [55]	Fatigue	" <b>Tiredness</b> , specifically, feeling <b>tired most of the time</b> in the previous month"	"Feeling tired most of the time."		Mortality rates at 10 years were 59% for older adults with fatigue, versus 38% for those without fatigue.
Agnihotri et al., 2007, Medicine [53]	Fatigue	The <b>subjective sensation of weakness, lack of energy, and tiredness.</b>	FACIT-F	Lack of hemoglobin was related to more fatigue	
Bellew & Fenter, 2006, Physical Therapy [9]	Muscular fatigue	Muscular fatigue is a reduction in the force generating <b>capacity</b> of muscle caused by recent	Performance based test		Fatigue was associated with decreased control of balance including

		activation and is considered a causative factor in <b>declining control of balance.</b>			modified Functional Reach Test, Lower-Extremity Reach Test, and Single-Limb Stance Time Test
Bennett et al., 2002, Nursing [83]	Fatigue	<b>Energy</b> , a common <b>symptom</b> that result from a variety of medical conditions in older adults	SF-36 vitality subscale		Fatigue serves as the mediator between medical conditions and physical functioning and role and social functioning

*Note.* 36-Item Short Form Survey (SF-36); Mobility-Tiredness (Mob-T); Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F); Fatigue Severity Scale (FSS); Visual Analogue Scale for fatigue (VAS-F); Multidimensional Fatigue Inventory (MFI); Center for Epidemiologic Studies-Depression (CESD); Cohen-Hoberman Inventory of Physical Symptoms (CHIPS); Pittsburgh Fatigability Scale (PFS); Brief Fatigue Inventory (BFI).

**Table 2.2** Descriptions of Identified Fatigue Measurements (n=25)

Author (year)	Instrument	Measure description
Avlund(2008) [59]; Avlund(2012) [46]; Bennett(2002) [83]; Broström (2018) [51]; Lin (2013) [19]	SF-36 vitality subscale	<b>Brief summary:</b> self-report frequency of energy and weariness over the past month <b>No. of items:</b> 4-item <b>Reliability:</b> 1) Internal consistency: Cronbach’s alpha 0.85 2) Test-retest reliability: N/A <b>Validity:</b> good criterion validity with a significant improvement in fatigue experienced the following rehabilitation intervention and discriminant validity between people with different outcomes. Construct validity scores on the SF-36 were significantly correlated with MOS SF-20.
Avlund(2008) [59]; Avlund(2011) [60]; Avlund(2012) [46]; Mänty (2014) [58]; Romine (2017) [17]	Mob-T	<b>Brief summary:</b> asking whether participants felt tired after the following tasks: transferring from a bed or chair, walking indoors, getting outdoors, walking outdoors in nice weather, walking out in poor weather, and climbing stairs <b>No. of items:</b> 6-item <b>Reliability:</b> 1) Internal consistency: reliable as items in the Mob-T Scale are homogeneous 2) Test-retest reliability: N/A <b>Validity:</b> good construct validity and concurrent validity and this measure was associated with diagnosed diseases and other functional measures
Agnihotri (2007) [53]; Tennant (2012) [44]	FACIT-F	<b>Brief summary:</b> self-reported fatigue and its impact upon daily activities and function in the past 7 days. <b>No. of items:</b> 28-item <b>Reliability:</b> 1) Internal consistency: Cronbach’s alpha 0.86-0.95 2) Test-retest reliability: 0.89 <b>Validity:</b> The FACIT Fatigue showed strong association with SF-36 Vitality ( $r = 0.73$ to $0.84$ ) and MAF ( $r = -0.84$ to $-0.88$ ), and the ability to differentiate patients.
Kim (2019) [52]; Tennant (2012) [44]	FSS	<b>Brief summary:</b> the severity of fatigue symptoms within the last week. <b>No. of items:</b> 10-item <b>Reliability:</b> 1) Internal consistency: Cronbach’s alpha 0.81-0.89 2) Test-retest reliability: 0.84 <b>Validity:</b> Correlation between FSS and FACIT Fatigue is $-0.825$
Lin (2014) [50]; Silva (2011) [4]	VAS-F	<b>Brief summary:</b> the subjective experience of fatigue “right now”. <b>No. of items:</b> 18-item <b>Reliability:</b> 1) Internal consistency: Cronbach’s alpha around 0.9 2) Test-retest reliability: N/A

Author (year)	Instrument	Measure description
Cho (2012) [47]; Liu (2019) [57]; Ha'gglund (2008) [83]	MFI	<p><b>Validity:</b> Correlation with FSS is 0.5 – 0.8</p> <p><b>Brief summary:</b> general fatigue, physical fatigue, reduced motivation, reduced activity, and mental fatigue.</p> <p><b>No. of items:</b> 20-item</p> <p><b>Reliability:</b> 1) Internal consistency: Cronbach's alpha &gt;0.8 2) Test-retest reliability: N/A</p> <p><b>Validity:</b> VAS-fatigue scores and MFI correlation ranged between 0.2 to 0.77.</p>
Soares (2015) [5];	Picked items from CESD Scale	<p><b>Brief summary:</b> the frequency of symptoms associated with depression, such as restless sleep, poor appetite, and feeling lonely over the past week</p> <p><b>No. of items:</b> unclear</p> <p><b>Reliability:</b> 1) Internal consistency: Cronbach's alpha N/A 2) Test-retest reliability: N/A</p> <p><b>Validity:</b> internal validity (a=0.860), sensibility (74.6%), specificity (73.6%)</p>
Whibley (2019) [48]	Picked items from CESD Scale	<p><b>Brief summary:</b> the frequency of symptoms associated with depression, such as restless sleep, poor appetite, and feeling lonely over the past week</p> <p><b>No. of items:</b> unclear</p> <p><b>Reliability:</b> 1) Internal consistency: Cronbach's alpha N/A 2) Test-retest reliability: N/A</p> <p><b>Validity:</b> internal validity (a=0.860), sensibility (74.6%), specificity (73.6%)</p>
Barbosa (2016) [62]; Moreh (2010) [18]	Tiredness questions	<p><b>Brief summary:</b> "Do you feel generally tired?" or "Level of tiredness"</p> <p><b>No. of items:</b> 1-item</p> <p><b>Reliability:</b> 1) Internal consistency: Cronbach's alpha N/A 2) Test-retest reliability: N/A</p> <p><b>Validity:</b> N/A</p>
Christie (2016) [83]	PROMIS-Fatigue	<p><b>Brief summary:</b> PROMIS measures provide a common metric for assessment of physical function, pain, fatigue, emotional distress, social function, and sleep/wake disturbance</p> <p><b>No. of items:</b> 7-item</p> <p><b>Reliability:</b> 1) Internal consistency: good reliability 2) Test-retest reliability: N/A</p> <p><b>Validity:</b> Construct validity was supported by moderate to strong correlations with legacy measures</p>
Hardy (2008) [55]	Tiredness questions	<p><b>Brief summary:</b> "Feeling tired most of the time"</p> <p><b>No. of items:</b> 1-item</p> <p><b>Reliability:</b> 1) Internal consistency: Cronbach's alpha N/A</p>

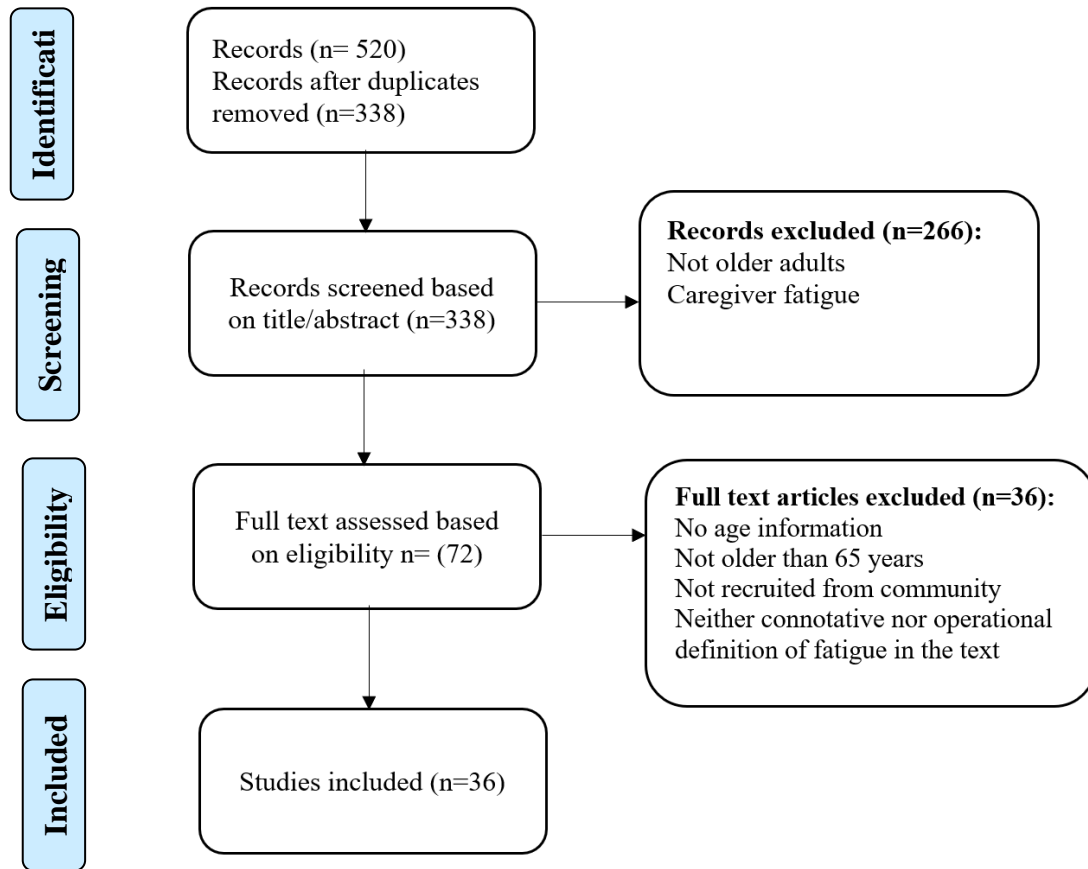
Author (year)	Instrument	Measure description
		2) Test-retest reliability: N/A <b>Validity:</b> N/A
Pérez (2019) [63]; Cooper et al., (2019) [70]	PFS	<b>Brief summary:</b> measure perceived physical and mental fatigability in older adults <b>No. of items:</b> 10-item <b>Reliability:</b> 1) Internal consistency: Cronbach's alpha 0.88 2) Test-retest reliability: 0.86 <b>Validity:</b> good convergent validity against physical performance measurements
Lindemann (2016) [67]	Fatigability	<b>Brief summary:</b> Measurements of decrease of maximum velocity of performance during repeated sit-to-stand transfers and the number of repetition when achieving a 10, 15, and 20 % fatigue threshold <b>No. of items:</b> maximum velocity of sit-to-stand performance <b>Reliability:</b> 1) Internal consistency: Cronbach's alpha N/A 2) Test-retest reliability: N/A <b>Validity:</b> N/A
Bellew & Fenter (2006) [9]	Fatigue	<b>Brief summary:</b> Measurements of static and dynamic balance control before and after fatiguing the ankle and knee <b>No. of items:</b> Fatigue Protocol (Fatigue was induced by using an isokinetic dynamometer. Balance testing was repeated immediately after the onset of muscular fatigue). <b>Reliability:</b> 1) Internal consistency: Cronbach's alpha N/A 2) Test-retest reliability: N/A <b>Validity:</b> N/A
Goldman (2008) [42]	Subscale from Revised Piper Fatigue	<b>Brief summary:</b> behavioral/severity, affective meaning, sensory, and cognitive/mood. It also contains open-ended questions to assess patients' beliefs about what contributes to their fatigue and what they do to alleviate their fatigue. <b>No. of items:</b> 5-item <b>Reliability:</b> 1) Internal consistency: Cronbach's alpha was high 2) Test-retest reliability: N/A <b>Validity:</b> The concurrent validity was moderate
Valentine (2009) [66]	Items from the CHIPS questionnaire	<b>Brief summary:</b> "constant fatigue" and "feeling low in energy" over the last two weeks <b>No. of items:</b> 2-item <b>Reliability:</b> 1) Internal consistency: Cronbach's alpha = 0.88 2) Test-retest reliability: N/A <b>Validity:</b> CES-D is moderately correlated with CHIPS

<b>Author (year)</b>	<b>Instrument</b>	<b>Measure description</b>
Hardy (2010) [45]	Items from literature	<b>Brief summary:</b> physical (sleepiness, low energy, weakness) and mental (emotional, cognitive) <b>No. of items:</b> N/A <b>Reliability:</b> 1) Internal consistency: Cronbach's alpha N/A 2) Test-retest reliability: N/A <b>Validity:</b> N/A
Chou (2012) [54]	4 items from Revised Clinical Interview Schedule	<b>Brief summary:</b> frequency of lack of energy and tiredness in the past week <b>No. of items &amp; Time:</b> 4-item <b>Reliability:</b> 1) Internal consistency: Cronbach's alpha was high 2) Test-retest reliability: N/A <b>Validity:</b> The validation coefficients for the fatigue scale, using an arbitrary cut off score of 3/4 and the item on the CIS-R were: sensitivity 75.5 and specificity 74.5.
Kwag (2011) [56]	Fatigue Scale as part of the Eight State Questionnaire	<b>Brief summary:</b> It measures 8 important emotional states and moods. <b>No. of items:</b> 12-item <b>Reliability:</b> 1) Internal consistency: good as all six of the Fatigue items exhibited significant loadings as predicted 2) Test-retest reliability: N/A <b>Validity:</b> 8SQ Fatigue subscale was acceptable as a discrete mood-state construct
Schnelle (2012) [49]	"Report change in energy"	<b>Brief summary:</b> change in energy <b>No. of items:</b> 1-item plus performance <b>Reliability:</b> 1) Internal consistency: Cronbach's alpha N/A 2) Test-retest reliability: N/A <b>Validity:</b> N/A
Shuman-Paretsky (2014) [6]	BFI	<b>Brief summary:</b> 1) fatigue severity at current, usual, and worst levels; 2) fatigue interference with daily activities, including general activity, mood, walking ability, normative work (both inside and outside the home), relations with other people, and enjoyment of life over the past 24 hours. <b>No. of items:</b> 9-item <b>Reliability:</b> 1) Internal consistency: $\alpha = 0.82 - 0.87$ for fatigue subscales and 0.96 for overall fatigue 2) Test-retest reliability: N/A <b>Validity:</b> good construct validity and criterion validity with SF-36
Shuman-Paretsky (2017) [43]	State-Trait Inventory of	<b>Brief summary:</b> a pool of items was formed from a review of the literature <b>No. of items:</b> 32-item <b>Reliability:</b> 1) Internal consistency: $\alpha=0.85 - 0.93$

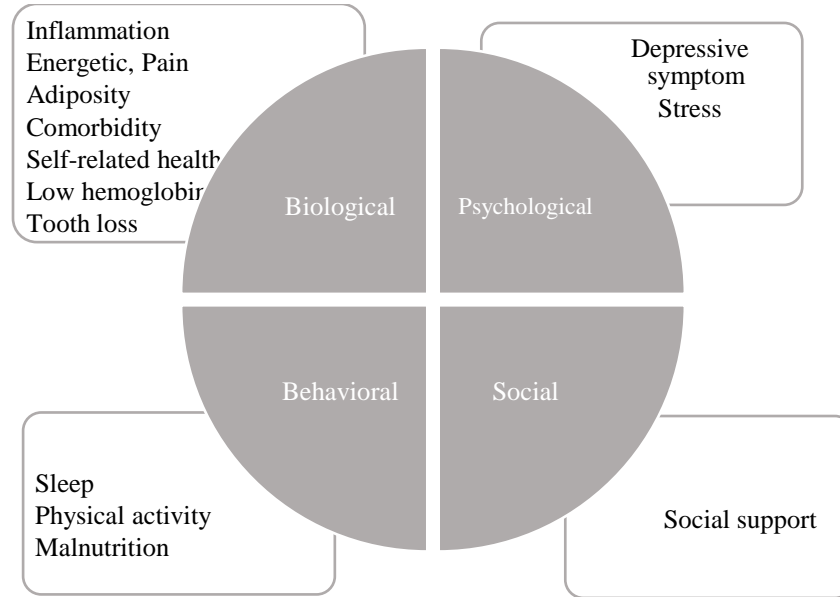
Author (year)	Instrument	Measure description
	Cognitive Fatigue	2) Test-retest reliability: N/A <b>Validity:</b> There was good convergent validity as measured by the strong positive relationship between cognitive fatigue and a subjective measure of general fatigue
Barak (2020) [65]	Self-created fatigue severity measurement	<b>Brief summary:</b> level of energy and the ability to do normal day-to-day activities <b>No. of items:</b> 1-item <b>Reliability:</b> 1) Internal consistency: Cronbach's alpha N/A 2) Test-retest reliability: N/A <b>Validity:</b> N/A
Baskurt (2012) [64]	Checklist Individual Strength - Turkish version	<b>Brief summary:</b> fatigue-related problems respondents might have experienced in the past 2 weeks. <b>No. of items:</b> 20 -item <b>Reliability:</b> 1) Internal consistency: $\alpha=0.84 - 0.95$ 2) Test-retest reliability: $r=0.74 - 0.86$ <b>Validity:</b> Concurrent validity was assessed (correlations with other fatigue scales were moderate to high).
Mänty (2014) [58]	Self-created "experienced feelings of general fatigue"	<b>Brief summary:</b> level of general fatigue during the past 14 days <b>No. of items:</b> 1-item <b>Reliability:</b> 1) Internal consistency: Cronbach's alpha N/A 2) Test-retest reliability: N/A <b>Validity:</b> N/A

*Note.* 36-Item Short Form Survey (SF-36); Mobility-Tiredness (Mob-T); Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F); Fatigue Severity Scale (FSS); Visual Analogue Scale for fatigue (VAS-F); Multidimensional Fatigue Inventory (MFI); Center for Epidemiologic Studies-Depression (CESD); Cohen-Hoberman Inventory of Physical Symptoms (CHIPS); Pittsburgh Fatigability Scale (PFS); Brief Fatigue Inventory (BFI); the Patient-Reported Outcomes Measurement Information System (PROMIS).

**Figure 2.1** The PRISMA-ScR Flow Diagram for the Review Process Detailing the Database Searches, the Number of Abstracts Screened, and the Full Texts Retrieved



**Figure 2.2** A Summary of Related Factors and Consequences of Fatigue in Community-Dwelling Older Adults from the Included Studies



**Supplementary Table 2.1** Search terms and results in four databases

<b>Keywords combination</b>	<b>Databases</b>	<b>Results</b>
("Fatigue"[Mesh] OR fatigue[ti]) AND ("Independent Living"[Mesh] OR "community-dwelling" OR "independent living" OR "aging in place") Filters activated: Humans, English, Aged: 65+ years	PubMed	199
((MH "Fatigue") OR TI fatigue) AND ((MH "Community Living") OR "independent living" OR "community dwelling" OR "aging in place") English, Aged: 65+ years, abstract available	CINAHL	172
(DE "Fatigue" OR TI fatigue) AND (DE "Aging in Place" OR "independent living" OR "community dwelling" OR "community living") English, Aged: 65+ years	PsycINFO	59
TITLE (fatigue) AND TITLE-ABS-KEY ( "independent living" OR "community dwelling" OR "aging in place" ) AND ( LIMIT-TO ( LANGUAGE , "English" ) )	Scopus	90

**Chapter 3. Application of isocaloric substitution analysis in nursing research: Exemplars from the Women's Health Initiative study**

## **Abstract**

Even though nurses often engage in nutrition care, nutrition-related research is underrepresented in nursing science. A lack of awareness of methods used to study nutrition may be one of the barriers to advancing this work. The purpose of this paper was to describe the Isocaloric Substitution Method (ISM) for studying nutrition and provide a real data example where we applied ISM to model tradeoffs between several nutritional choices in terms of their relationship with fatigue among women aged 65+ enrolled in the Women's Health Initiative (WHI) study. We illustrated the use of different types of ISMs including partition, standard multivariate, residual, and multivariate density methods. The results showed that substituting one ounce of cooked lean red and processed meat with an equivalent amount of fish, nuts, and legumes, respectively, was associated with improvement in fatigue. The results were consistent across partition, standard multivariate, and residual methods. In the multivariate density method, which used macronutrients rather than individual foods as exposure variables, substituting vegetable protein for animal protein for 5% of total energy was associated with improvement in fatigue. Data were also analyzed with food and nutrients coded as categorical rather than continuous metrics, and the results were similar across methods. In conclusion, this is the first methodological paper to introduce ISM to nursing research with both food and nutrient substitution as an exemplar, which will help nursing researchers understand the strengths and limitations of the ISMs and facilitate collaborations with nutrition scientists and statisticians concerning new methods to study nutrition.

(250 words)

**keywords:** isocaloric substitution, fatigue, older women

## **Introduction**

Unhealthy eating is associated with obesity, chronic diseases, and deaths. Specifically, unhealthy eating habits have contributed to the obesity epidemic in the United States (Ogden & Carroll, 2010; Ogden et al., 2014; Ogden et al., 2016). An unhealthy/poor diet is ranked as the number one risk factor for deaths in the U.S., surpassing tobacco and high blood pressure (Afshin et al., 2019), and it also contributes to some leading causes of death such as heart disease, diabetes, cerebrovascular disease, and cancer (Xu et al., 2014). In older adults, their eating behavior is compounded by physiological and psychosocial factors (e.g., cognition and memory), which put older adults at a higher risk of health issues. Given the close link between poor diet and adverse health, healthy nutrition is critical.

In clinical practice, nurses routinely engage in nutrition care and promote healthy nutrition. Nurses often fill the role of counselors of nutrition by providing nutrition screening and nutrition advice (Xu et al., 2017). Nutrition is an integral part of nursing, but, for the most part, nutrition is still underrepresented in nursing research (Im et al., 2020). While different factors might account for this gap, a lack of awareness of methods used to study nutrition may be one of the modifiable barriers. The Isocaloric Substitution Method (ISM) is one method to study diet that could be pertinent for nursing science because it helps understand the tradeoff between different nutritional choices with regard to health outcomes, which could inform nutritional advice. In this paper, we will describe the ISM and provide a real data tutorial on how to use this method by using data from the Women's Health Initiative Long Life Study (WHI LLS) (Women's Health Initiative Study Group, Sep 14, 2021). Of note, while the ISM is inherently transdisciplinary and according to NIH 2020-2030 strategic plan, nutrition is a cross-cutting topic across many NIH Institutes/Centers (IC), National Institute of Nursing Research (NINR) is still falling behind several IC such as National Institute of Diabetes and Digestive and Kidney

(NIDDK) and National Center for Complementary and Integrative Health (NCCIH) in nutrition focused research. As such, adding another tool to the current skillset of nutrition-related methods, nurse scientists may be strengthening their role in this area.

### **Types of ISM**

ISM, by its nature, is a linear regression ( Willett, 2012; Willett et al., 1997). The word “substitution” originally appeared in the domain of economics, when the demand for a good changed because of the higher price; thus, consumers switched away from the good toward its substitutes. Subsequently, substitution analysis has been widely used to study nutrition, physical activity, and other domains like geology. Substitution is achieved by including both the nutrients of interest and the total energy intake as independent variables. As such, in ISM, the coefficient of the nutrient variable represents the effect on an outcome when substituting the nutrient for an excluded nutrient; the coefficient of total energy intake refers to a change of outcome from nutrients excluded from the model, while keeping total energy intake constant. ISM removes confounding effects from total energy intake, allows for the study of multiple nutrients/food groups, and alters macronutrient composition while holding total energy constant to identify the optimal diet, thus ISM can serve as another method to triangulate results in instances when randomized clinical trial (RCT) is not available. There are four ISMs: partition method, standard multivariate method, residual method, and multivariate density method (Willett et al., 1997). Typically, the partition method, standard multivariate method, and residual method are used to study food groups and macronutrients, while the multivariate density method is mostly used to study macronutrients, because recommendations of food groups in Healthy Eating Guidelines are given in absolute amounts (e.g., serving, ounce, cup) instead of relative amounts (e.g., 5% of vegetables or fruits). In addition, the percentage of vegetables or fruits has a varied meaning as

different individuals usually have widely different vegetables or fruits. The ensuing introduction provides an overview of the four ISMs.

A partition method is an approach in which energy terms such as fat, protein, carbohydrate, and alcohol are used for input. This method does not control for total energy intake (in food analysis, it does not control for the entirety of food consumption); thus, it might not be considered as an “isocaloric method” *per se*. The method is generally used to study the dynamics of adding one nutrient while keeping the other nutrients constant (Willett et al., 1997). Although the substitution effect may be calculated (the coefficient of nutrient in the model minus the coefficient of nutrient that will be replaced), the standard error of substitution cannot be easily evaluated without knowledge of the covariance of the estimated regression coefficients.

A standard multivariate method is an approach in which total energy intake and the nutrients of interest are included and the nutrient variable substituted for is excluded. This method is typically used to investigate the effect of substituting one nutrient while holding total energy constant. When the nutrient intake and total energy intake are highly collinear, adding these two variables simultaneously to the model may significantly reduce their individual variability and the biological meaning of the nutrient could change (Willett et al., 1997). Therefore, the method applies to a sample when the nutrient and total energy variables are weakly correlated.

A residual method is a method in which total energy intake and the residual of each nutrient variable of interest are entered, with nutrient residuals providing a measure of nutrient intake uncorrelated with total energy intake. In residual methods, each individual nutrient variable is regressed on the variable of total energy intake. The residuals from the regression represent the differences between actual intake and the intake predicted by their total energy

intake. Residual methods can be used to study the effect of substituting one nutrient for another or adding both one nutrient and "other" nutrients in a specific proportion (Willett et al., 1997). A residual method inspects the nutrient effect that is independent of total energy and does not change the biological meaning of total energy so that it can be widely used in the analysis of various nutrients. When nutrient variables were coded as continuous variables, the standard multivariate, energy partition, and residual models are statistically interchangeable (Kushi et al., 1992; Brown et al., 1994).

A multivariate nutrient density method is a method in which the computed nutrient density of interest and total energy are used for input. This method generally is used to examine the outcome difference associated with percentage change in an exposure measure, while total energy intake is kept constant. Because changing the same amount of nutrient density should theoretically be different for individuals of varying body types, the multivariate nutrient density method that focuses on the relative ratio of dietary components to total energy is especially suitable when there are large differences in body size between individuals (Willett et al., 1997).

### **Application and the specifications of ISM**

ISM can be used to study both macronutrients and food groups in relation to health outcomes and has been widely used for this purpose. Examples of food groups in relation to different outcomes may be found in Hansen et al. (2020), Huang et al. (2020), and Pan et al. (2012). Illustrations of macronutrients in relation to outcomes include Hu et al. (1999), Meisinger et al. (2019), and Song et al. (2016).

To apply ISM in analysis, several specifications should be considered. In macronutrient analysis, both energy-yielding nutrients (i.e., fat, carbohydrate, and protein) and alcohol should be included in the model because although alcohol is not a macronutrient, it contributes 7 cal/g

energy. Additionally, it is necessary to specify the food sources of macronutrients, as within each macronutrient there are both “bad” and “good” components. Although it is proper to study the low-fat diet or high protein diet without specifying food sources of macronutrients, over the decades, the composition of macronutrients shifted from vegetable protein to more animal protein, from cheap carbohydrate to animal fat and protein (Logan, 2006); thus, it is vital to specify food sources of macronutrients and examine tradeoffs between and within macronutrients.

Food group modeling is more nuanced than macronutrients, and more specifications should be considered: 1). While nutrients are preferred in the unit of kcal, food groups can be in any unit like frequency, amount, serving, or grams (Song & Giovannucci, 2018). 2). Selected foods should be associated with the outcome of interest in light of previous studies (Doaei et al., 2017). 3). The foods being substituted should be commonly consumed (Song & Giovannucci, 2018). 4). Food being replaced should have a reasonable comparable range; otherwise, the estimated effect would be too difficult to be practiced in real life (Song & Giovannucci, 2018). 5). Food items included in substitution analysis should differ from each other concerning their food ingredients that affect the desired outcome (Doaei et al., 2017). 6). Substitution analysis is better for two food groups when only one food group has independent benefits. If both food groups have independent benefits, it is better to add both foods rather than substitution (Song & Giovannucci, 2018). 7). It is essential to adjust for confounding variables, namely the variables that closely relate to eating behavior and also are significant risk factors of the outcome variable, to increase the internal validity of the research (Doaei et al., 2017).

### **Application of ISMs to the analysis of fatigue in WHI LLS data**

In this article, we present the utility and real data application of ISM using a large cohort of American women aged 65 and older enrolled in the WHI LLS. We chose to focus on the protein and fatigue relationship because although protein correlates with fatigue (Wu, 2016), intervention studies show conflicting results regarding protein effects on fatigue (Bhasin et al., 2018; Reule et al., 2017; Schoufour, 2019). The inconsistent findings may be due, at least partially, to not specifying protein source or confounding by other macronutrients and total energy values (Schoufour et al., 2019). The availability of Food Frequency Questionnaire data in the WHI provides an opportunity to quantify consumption of both plant and animal protein sources and specify foods to measure the relationship between protein and fatigue among older women. Specifically, we focused on these food groups: fish, poultry, nuts, legumes, eggs, and red and processed meat, because these six food groups constitute the primary sources of protein foods in the US (USDA ChooseMyPlate, n.d.), and the tradeoffs among these food groups is reasonable tradeoffs because the tradeoffs of these food groups (i.e., fish, poultry, nuts, legumes, low-fat dairy, and whole grains substitute for red meat) has been studied previously in relation to mortality (Pan et al., 2012).

The objective of using this example is to demonstrate how the ISM approach can be used to examine the tradeoffs between different food choices/macronutrients and estimate their relationship to changes in fatigue. Specifically, we illustrated the substitution among food groups (i.e., fish, poultry, nut, legumes, and eggs for red and processed meat) using partition method, standard multivariate method, and multivariate residual method. Next, we demonstrated substitution analysis among macronutrients using only the multivariate density method.

## **Methods**

### **Participants**

This study uses an observational cross-sectional design. Participants were those who enrolled in both Objective Physical Activity and Cardiovascular Disease Health (OPACH) Study (LaCroix et al., 2017) and WHI-Food Intake (WHI-FI) (Beasley et al., 2020), two ancillary studies of the Women's Health Initiative (WHI) study (Design of the Women's Health Initiative Clinical Trial and Observational Study, 1998). The WHI LLS was conducted to collect data on healthy aging and cardiovascular risk factors during the second Extension Study of the WHI among a subcohort of 7,875 WHI participants from 2012 to 2013 from all 40 original US clinical centers (Women's Health Initiative Study Group, Sep 14, 2021), among whom 7,048 women consented to participate in the OPACH study, which focused on actigraphy data. The WHI LLS participants also received an invitation to participate in a WHI-FI Study in which they received a Food Frequency Questionnaire (FFQ). A total of 6,094 FFQs were mailed back. For the current study, we first retained 6,489 OPACH participants who returned their accelerometer, provided usable data, and were older than 65. Among the 6489 women, 4812 completed FFQs for WHI-FI, and 4563 reported plausible average energy intakes, defined as  $\geq 600$  kcal /day and  $\leq 5,000$  kcal /day (Beasley et al., 2020; Willett, 1998). These 4,563 women composed our final analytical sample. The Fred Hutchinson Cancer Research Center Institutional Review Board approved the WHI-FI study protocol, and all participants provided written informed consent. A flow chart is seen in **Figure 3.1**.

### **Measures**

The FFQ has 124 items, with an additional 13 adjustment questions pertaining to fat intake, fortification of juices consumed, and type of cold cereal consumed. Nutrient calculations based on reported intake were performed using the Nutrition Data System for Research software version 2012, developed by the Nutrition Coordinating Center, University of Minnesota

(Nutrition Data System for Research, 2012). Total energy intake was calculated as:  $4 \text{ (kcal/gram)} * \text{carbohydrate (gram/day)} + 4 \text{ (kcal/gram)} * \text{protein (gram/day)} + 9 \text{ (kcal/gram)} * \text{fat (gram/day)} + 7 \text{ (kcal/gram)} * \text{alcohol (gram/day)}$  (Meisinger et al., 2019). Fish, poultry, and red and processed meat were in the unit of ounces of cooked lean meat; nuts, legumes, and eggs were in the unit of ounce equivalents of lean meat. Protein foods were calculated as the sum of the six protein food groups (USDA ChooseMyPlate, n.d.). To maximize statistical power, food groups, macronutrients, and total energy intake were all coded as continuous variables. Then, the food and nutrient exposures were categorized as tertile variables only to illustrate the concrete procedures needed for categorized nutrient or food variables.

The RAND-36 Vitality subscale was used to measure fatigue (Ware & Sherbourne, 1992). The Vitality subscale comprises four questions that ask about the frequency of having a lot of energy and feeling tired, worn out, and full of pep over the previous four weeks, with item responses ranging from 1 (all the time) to 6 (none of the time). Fatigue was calculated as the mean score of the four questions. Fatigue was then recoded to range from 0 to 100, with a higher score representing a more favorable health status (Hays et al., 1993; Ware & Sherbourne, 1992). The Vitality subscale is reported as the most commonly used measure among community older adults, with good reliability, criterion validity, and discriminant validity (Su, Cochrane, Yu, et al., 2022). In the current study, the reliability is 0.86.

A list of covariates was provided, including age, ethnicity, education, health-related variables, Body Mass Index (BMI), diabetes, and physical activity. Physical activity was based on accelerometry data and included time spent in low-light (19–225 counts/15s), high-light (226–518 counts/15s), and moderate to vigorous ( $\geq 519$  counts/15s) intensity levels (Evanson et al., 2015). The health conditions covered self-rated health (Ware & Sherbourne, 1992), mental

health (i.e., depression measured by a shortened version of the Center for Epidemiological Studies Depression Scale) (Burman et al., 1988), and the number of self-reported chronic diseases (i.e., the sum of COPD, CVD, cerebrovascular disease, cancer, osteoarthritis, and cognitive impairment). Age, self-rated health, depressive symptoms, and the number of chronic diseases were from WHI or LLS questionnaires proximal to the OPACH study baseline. Data from the 2000 census were used to assess Neighborhood Socioeconomic Status (NSES) at the census tract level. NSES was an index of the six census tract variables: (1) percent of those older than 25 with the education less than high school; (2) percent of male unemployment; (3) percent of households whose income are below the poverty line, etc. The NSES index was considered a continuous variable ranging from 0 to 100 for US census tracts; higher scores indicated more affluent tracts (Bird et al., 2010; Dubowitz et al., 2008; Merkin et al., 2009). The details about the choice of the covariates can be found elsewhere (Su, Cochrane, Reding, et al., 2022).

## **Statistical analysis**

### **Data preparation**

First, we checked all specifications for food group substitution and learned that fish, poultry, nuts, legumes, eggs, and red and processed meat represent commonly consumed but distinct food groups and all are expressed in the unit of ounce. The six food groups are under the category of protein foods, and all are main sources of protein. Based on previous knowledge, protein is an important correlate to fatigue among older adults (Wu, 2016). From previous research, certain food groups are considered more beneficial than other groups in relation to health. Thus, the specifications of food substitution are appropriate. Second, the total energy and each macronutrient were calculated using the following equation (Meisinger et al., 2019):

$$Total\_energy = carbohydrate * 4 + protein * 4 + fat * 9 + alcohol * 7$$

$$protein\_energy = protein * 4$$

#### Four methods

*Partition Method.* A partition method including food categories takes this form:

Fatigue =  $\alpha_0 + \alpha_1 * fish + \alpha_2 * poultry + \alpha_3 * eggs + \alpha_4 * nuts + \alpha_5 * legumes + \alpha_6 * red\_processed\_meat + \varepsilon$ . (*Note:* A list of covariates was included in the model but not shown in the equation).  $\alpha_1$  represents the effect of increasing fish by one unit while keeping other protein foods unchanged. Similarly,  $\alpha_6$  represents the effect of increasing red and processed meat by one unit.  $\alpha_1 - \alpha_6$  represents the effect of substituting fish for red and processed meat (Willett, 2012). However, in the testing of the null hypothesis, we do not really know if  $\alpha_1$  differs from  $\alpha_6$  since both are estimates. Thus, even though the substitution effect can be calculated from this method, the significance of the effect is unclear.

*Standard Multivariate Method.* A standard multivariate method including food categories takes this form: Fatigue =  $\beta_0 + \beta_1 * fish + \beta_2 * poultry + \beta_3 * eggs + \beta_4 * nuts + \beta_5 * legumes + \beta_6 * T + \varepsilon$ , where  $T$  refers to the total amount of protein foods and  $T = fish + poultry + nuts + legumes + eggs + red\ and\ processed\ meat$ . (*Note:* A list of covariates was included in the model but not shown in the equation).  $\beta_1$  represents the effect of increasing fish by one unit while keeping  $T$ , poultry, nuts, leagues, and eggs unchanged, which can only be achieved by a simultaneous reduction of red and processed meat by one unit. Thus,  $\beta_1$  represents the effect of substituting fish for red and processed meat while keeping total protein foods constant. Similarly,  $\beta_6$  represents the effect of increasing entire protein foods by one unit while keeping fish, poultry, nuts, legumes, and eggs constant, which is equivalent to increasing red and processed meat by one unit, the same effect as  $\beta_6$  in the partition model. Thus,  $\beta_6$  represents the effect of increasing red and processed meat (Willett, 2012).

*Residual Method.* In this procedure, each food group is regressed on total protein foods  $T$  to get a residual. Because food/nutrient intake is usually highly skewed towards high values (Hu et al., 1999), transformations, such as taking logarithms of the nutrient or food variables, are typically used to create residuals with a more constant variance across the independent variable. The use of a logarithmic transformation means that nutrient intake is now expressed as a proportional difference. The residuals (*i. e.*,  $R_{fish}$ ,  $R_{poultry}$ ,  $R_{nuts}$ ,  $R_{legumes}$ ,  $R_{eggs}$ ) represent the differences between each food group and the food group predicted by  $T$ . The residual model takes this form:  $Fatigue = \gamma_0 + \gamma_1 * R_{fish} + \gamma_2 * R_{poultry} + \gamma_3 * R_{eggs} + \gamma_4 * R_{nuts} + \gamma_5 * R_{legumes} + \gamma_6 * T + \varepsilon$ . (*Note:* A list of covariates were included in the model but not shown in the equation). The interpretation of each residual coefficient is identical to that in the standard multivariate model, however,  $\gamma_6$  represents the effect of increasing calories from fish, poultry, nuts, legumes, eggs, and red and processed meat by a specific proportion. Because residuals have a mean of zero, a constant  $C$  can be added to every value to convey the sense of an actual food intake. The constant  $C$  is arbitrary statistically but could be the predicted nutrient intake at the mean intake of total protein foods.  $R_{fish}$  or  $R_{fish} + C$  is also called a calorie-adjusted nutrient intake (Willett et al., 2012).

*Multivariate Density Method.* Like the other three methods, the multivariate nutrient density method also excluded one macronutrient and included total energy intake in the model, but the difference in each macronutrient is in the form of a percentage. The density method takes

this form:  $Fatigue = \delta_0 + \delta_1 * \frac{vegetable\ protein\ energy}{total\ energy * 0.01} + \delta_2 * \frac{fat\ energy}{total\ energy * 0.01} + \delta_3 * \frac{carbohydrate\ energy}{total\ energy * 0.01} + \delta_4 * \frac{alcohol\ energy}{total\ energy * 0.01} + \delta_5 * total\ energy + \varepsilon$ , where *totalenergy* refers

to total energy intake and  $totalenergy = animal\ protein\ energy + vegetable\ protein\ energy + carbohydrate\ energy + fat\ energy + alcohol\ energy$ ,

with each variable in the unit of calories. The meaning of the coefficient for the nutrient density is the difference in outcome associated with a change in 1% of energy from the nutrient while total energy intake is kept constant. Conventionally, variables for fat, protein, carbohydrate, and alcohol were appropriately scaled, such that coefficients for energy-providing nutrients denote a change per 5% of total energy intake (5E%) (Meisinger et al., 2019), which corresponds to an energy intake of about 100 calories, assuming an adult's energy intake of 2,000 calories. Thus, the estimated coefficient of vegetable protein can be interpreted as the change of fatigue with vegetable protein substituted for animal protein for a 5%E, while holding total energy, all other sources of energy supply and all confounders constant. The rescale process can be achieved with the following equation:

$$vegetable\_Protein\_5percent = vegetable\_Protein\_energy / (0.05 * Total\_energy)$$

### **Categorization of nutrient variables**

In practice, to address a nonlinear relationship between nutrient/food and outcomes, it is common to code nutrient/food variables as categorical variables to evaluate outcome change in different groups (Willett, 2012). In that case, the quantile of each food/nutrient variable in the partition and standard multivariate models and the quantile of energy-adjusted nutrient intake in the residual model will be created. The coefficient of fish in the standard multivariate model refers to the effect on fatigue when substituting enough fish for red and processed meat in a subject's diet so that the subject will be taken out of the first and into the second quartile of absolute fish intake. In the residual method, the coefficient of fish represents the effect of substituting enough fish for red and processed meat to move the subject from the first to the second quartile of energy-adjusted fish intake.

### **Data preparation after ISM specification**

After the ISMs were established, we checked the assumptions of linear regression. The linearity assumption was checked with residual plots and the normality of distributed errors was checked with Q-Q plots. Both assumptions were appropriately met. Next, missing patterns were checked among the list of covariates (i.e., age, ethnicity, education, self-rated health, depression, BMI, number of chronic diseases, sleeping hours, social support, total energy, diabetes, NSES, low light physical activity time, high light physical activity time, moderate to vigorous physical activity time, the total energy intake), and all variables had missingness less than 10%; thus, multiple imputations were adopted. The multiple imputation was based on the maximizing expectation method to account for missing data in dependent and independent variables (King et al., 2001). To optimize the approximation, some food groups and nutrient variables not in the list of covariates served as auxiliary variables in generating our ten imputed datasets. In food analysis, nutrient variables served as auxiliary variables in the imputed model but not as covariates of the analysis model. To avoid perfect collinearity, not all variables entered the imputed model to generate imputed dataset; thus, for each method, the imputed dataset is not exactly the same. Models were run on each of the ten imputed datasets, and then parameter estimates and variances were calculated based on Rubin's rule (Little & Rubin, 2002; Rubin, 2004). All analyses were performed with RStudio (RStudio Team, 2018).

### **Results**

As shown in **Table 3.1**, the women in the analysis were on average aged 78.9 years, and more than 90% reported themselves as having good or very good health status. Approximately 53% were White women. The composition of energy from fat, carbohydrate, protein, and alcohol was 31%, 50%, 16%, and 2%, respectively. The daily consumption of nuts, legumes, eggs, fish, poultry, red and processed meat, and total protein were 0.94, 0.40, 0.37, 0.74, 0.84, 1.61, and 4.90 ounce equivalents for the current sample. The correlations ranged from 0.05 to 0.2 among

food groups and from 0.7 to 0.9 among macronutrients and total energy intake. Correlations between total energy intake and specific foods were below 0.5 ( $p < .001$ ) and between total energy and fatigue were around -0.1 ( $p < .001$ ) (see **Supplementary Tables 3.1 & 3.2**).

As shown in **Tables 3.2 & 3.3**, when models were not controlling for total energy intake, increasing red and processed meat (-0.62, 95%CI: -0.97 ~ -0.26) and poultry (-1.2, 95%CI: -1.88 ~ -0.53) was associated with worsening of fatigue; increasing fish (1.10, 95% CI: 0.46 ~1.73) and legumes (0.81, 95%CI: 0 ~ 1.61) was associated with improvement of fatigue. In the partition model, the estimated fatigue change associated with a one-ounce increase was stronger for increased fish intake (1.27, 95% CI: 0.62 ~1.93) than for legumes (1.13, 95% CI: 0.23 ~ 2.03), poultry (-1.04, 95% CI: -1.77 ~ -0.31), egg (-0.81, 95%: -1.83 ~ 0.22), nuts (0.44, 95% CI: -0.04 ~ 0.92), or red and processed meat (-0.41, 95% CI: -0.81 ~ -0.01). Hence, for the same amount of increased food, the different food intakes were associated with different fatigue changes. Moreover, calculating the difference in coefficients for the foods being compared in the partition model (e.g., fish – red and processed meat =  $1.27 - (-0.41) = 1.68$ ) is equivalent to substituting fish for red and processed meat.

In the standard multivariate model, substituting one ounce cooked lean red and processed meat with the same amount of fish, nuts, and legumes was associated with 1.68 (95% CI: 0.97 ~2.40), 0.85 (95% CI: 0.27 ~1.42), and 1.54 (95% CI: 0.6 ~ 2.48) improvements in fatigue. The coefficient of total protein variable represents the impact on fatigue due to red and processed meat, and it showed that simply increasing red and processed meat was associated with worse fatigue -0.41(95%CI: -0.81 ~ -0.01).

When we ran the residual model, it was noticed that the distribution of food groups was skewed toward higher values and some participants reported zero intakes of certain food groups,

so residuals were greater at higher total nutrient intake. While it is completely reasonable to have zero intake of certain food groups, it is impossible to log transform the food variables with zero as intakes. In the current paper, to illustrate the residual model with a real data example, we illustrated it with food variables as continuous and without transforming. Notably, the coefficients in the residual model were identical to those in the standard multivariate model except for the coefficient of total protein variable, which keeps the biological meaning and refers to the effect on fatigue from increasing food groups (fish, poultry, nuts, legumes, eggs) and red and processed meat in the specific proportions, and it was nonsignificant 0.01(-0.24, 0.26).

As shown in the multivariate density model (**Table 3.4**), substituting vegetable protein for animal protein for 5% of total energy was associated with 2.40 (95%CI: 0.86 ~ 3.94) points improvement in fatigue. It was not of initial interest, but it was noticeable that substituting fat for animal protein for 5% of total energy was associated with 1.11 (95%CI: -1.9 ~ -0.27) points worsening of fatigue. The total energy coefficient retains the biological meaning and refers to the effect on fatigue from increasing all macronutrients synchronously, which has almost no impact on fatigue (0, 95%CI: 0 ~ 0).

When food variables were categorized, significant predictors were not the same as those when foods and nutrients were continuous (i.e., legumes were significantly related to better fatigue scores when in continuous but not categorical form; egg was significantly related to worse fatigue when in categorical but not in continuous form), but all yielded similar substantive results. That is, fish was favorably associated with fatigue, whereas red and processed meat was unfavorably associated with fatigue; substituting fish, nut, and legumes for red and processed meat related to fatigue improvement, plant protein for animal protein was related to fatigue improvement, and fat for animal protein was related to fatigue worsening.

## **Discussion**

This is the first methodological paper to introduce isocaloric substitution methods to nursing research with both nutrient and food as an exemplar, which facilitates nursing researchers' familiarity with methods in studying nutrition and ultimately could promote more emphasis on nutrition in nursing research. The purpose of this article was to describe and illustrate the utility of ISM approaches in nursing research. We presented a step-by-step example of the ISM framework in which we examined tradeoffs between different foods and macronutrients in relation to fatigue. Specifically, we performed food analysis using partition, standard multivariate, and residual methods, and we conducted macronutrient analysis using a multivariate density method. We compared and contrasted findings from the different ISM approaches and provided an interpretation of the results.

### **Findings from ISMs**

ISMs in food analysis consistently showed the benefits of nuts, legumes, and fish on fatigue in replacing red and processed meat. Results from the multivariate density model that vegetable protein is preferable to animal protein concerning fatigue align with food analysis and confirm that fatigue improvement is related to substituting legumes or nuts for red and processed meat. When variables were categorized, the statistical interchangeability did not exist but showed similar substantive results. Our finding was consistent with previous randomized clinical trials in that a very low-fat, plant-based diet or a diet that recommended more intake of nuts, legumes, fish, and less red and processed meat significantly improved fatigue (Mousavi-Shirazi-Fard et al., 2020; Yadav et al., 2016). Compared with clinical trials, ISM can involve a large number of participants and allow researchers to simulate the composition of diets to identify an optimal combination before implementing the experiments. For example, by summing up poultry and red and processed meat as one variable, we can easily get the effect of when fish or legumes replace

all meat, and this improvement is independent of other protein foods, total protein foods, total energy, physical activity, and other covariates. RCTs to assess the pure effect of a particular food or nutrient may be to confine the analyses to those who consumed only the foods or nutrients of interest, which has many limitations. While doing so may control for confounding effects by other foods, the caveats are the decrease in sample size and the potential overlap among the different food groups (e.g., people who eat one particular food may also favor certain foods). Therefore, all these issues make the ISM particularly valuable.

The same results for food analysis from the three methods reflected the fact that when food variables were coded as continuous variables, the standard multivariate, energy partition, and residual models were statistically interchangeable. However, although the partition and the ISMs are mathematically equivalent, these models elucidate different perspectives on the relationship between different foods and fatigue. For example, although the physiologic benefits of one food may be similar across individuals, the actual overall impact of that food may have a wide range of effects, depending on each individual's foods limitations, choices, and general lifestyle. Hence, using ISM would eliminate such heterogeneity by carefully reframing the causal question as an ISM question of whether we eat one food not another for certain amount of total energy. In our results, we only illustrated the substitution of red and processed meat, but if other food groups were substituted, we would find that the same foods have different effects. Whereas one food may appear protective against fatigue if it displaces red and processed meat, the same food is not beneficial when replacing fish.

The finding from correlation table (**Supplementary Tables 3.1 & 3.2**) that total energy intake was significantly related to fatigue and confounding the effect of each protein food on fatigue suggests it is essential to control for total energy in nutrient/food analysis. The finding

from Table 3 standard method that total intake of protein foods was a significant but slight predictor of fatigue may be due to opposing effects of specific protein food sources. Despite the slight effect of total protein foods, it is essential to include the total protein food variable to induce the substitution effect. By including total energy intake and total protein foods in the models, we compared participants with similar energy intake and similar protein foods intakes but with different compositions of the diet. Failure to account for total energy intake and total intakes of protein foods may be misleading that being vegan might be related to fatigue, but the real reason may be undereating of total energy or undereating of total protein foods. Once total energy intake and total protein foods are held constant, it is more obvious to see the benefit of a plant-based diet. As shown in Table 3, when total energy intake was controlled for, the benefit of legumes increased and when the total protein intake was controlled for, the benefit of legumes increased again. Besides, daily energy intake is usually constant when the body size, physical activity, metabolic efficiency, and other factors like change in body fat are constant (Willett et al., 1997). All these provided a strong rationale for why ISM, which controls total energy or food consumption, is particularly valuable.

### **Detailed Consideration of ISM**

It was noted that the coefficient in the partition method has only one interpretation; however, the coefficients in the other three ISMs could have multiple interpretations depending on which variable is taken out of the model. Estimates from the partition method do not account for other foods' displacements, thus, rigorously, the partition method is not an ISM. However, a partition method is always presented whenever different types of ISMs are contrasted. The reason may be that ISMs only assess the effect of one nutrient in relation to another. For example, we may be able to provide evidence that carbohydrate is more protective than fat

intake, but we would never be able to say whether the carbohydrate prevents or the fat promotes disease (Freedman et al., 1997). Thus, a partition method is always introduced along with and serves as a supplementary method to ISMs.

When using a standard multivariate method, collinearity may be an issue. However, most authors consider the removal of confounding as more important and think that collinear variables of up to 0.90 can still be reasonably controlled in various models, as was previously done (Hu et al., 1999). A standard multivariate method uses absolute values, and it is easier to interpret and understand the tradeoffs. The substitution of absolute values has been widely used in research and considered as a gold standard to study physical activity (Mekary & Ding, 2019). Due to the low linearity among food groups, this method has been widely used in food analysis (Hansen, 2020, Pan et al., 2012). Even though the method can be used in nutrient analysis (Brown et al., 1994; Hu et al., 1999), most researchers choose residual or density methods to address collinear issues in macronutrient analysis.

In a residual method, although a log transformation of food or nutrient is suggested, due to the highly skewed nature of food groups and alcohol, only a few researchers have adopted log transformation in their analyses (Hu et al., 1999; Zhang et al., 2005), yet both studies neglected the energy-yielding effect of alcohol. Many researchers have adopted residual methods without particular emphasis on the distribution assumption and log transformation. The residual method has been widely used in both food (Talamini et al., 2006) and macronutrient analyses (Campmans-Kuijpers et al., 2015; Dai et al., 2017; Hrolfsdottir et al., 2016).

A density method in percentage form is consistent with national dietary guidelines and therefore can be directly translated into public health recommendations that are expressed in these units. Besides, the density method solves the collinear problem as indicated from

simulation tests that nutrient density is weakly correlated with total energy even when nutrient and total energy intake are highly correlated (Jovanovic et al., 1994; also see Supplementary Tables 3.1 & 3.2). Thus, a multivariate density method has been widely used with macronutrients (Campmans-Kuijpers et al., 2015; Meisinger et al., 2019; Zhang et al., 2005).

When the independent variables are categorical, because the between-subject variation in nutrient residual (i.e., energy-adjusted nutrient) is different from the between-subject variation in absolute nutrient intake, a different increase in nutrient intake is required to induce a step-up in a nutrient residual quartile compared with what is required to induce a step-up in an absolute nutrient quartile. This means that the statistical interchangeability of the standard multivariate, energy partition, and residual models does not apply (Kushi et al., 1992; Brown et al., 1994). While the statistical interchangeability of ISMs simplifies the method selection, when a nutrient or food is in the categorical form, researchers need to choose among ISMs for specific analysis. It was found the residual method and the multivariate density method were more robust in eliciting significant results. More details about this point can be found in other papers (e.g., Brown et al., 1994).

### **Limitations**

There are a few caveats to the application of ISMs. In a partition method, any observed association can still be confounded by total energy or food intake in the case of food analysis, and the comparative consumption of displaced food is not clear. In a standard multivariate method, one limitation is that substituting fish for red and processed meat in an equal amount might not necessarily lead to the inverse effect estimate when this substitution is reversed (substituting red and processed meat for fish; Mekary & Ding, 2019). In the residual method, a log transformation of nutrient or food groups is usually needed due to the high skewness towards

high values (Hu et al., 1999); however, few researchers did that due to the zero intakes. When a residual method is used for food analysis, although residuals are independent of total food intakes, the total food and total energy may be highly correlated. One caution of the density method is because the density variable consists of the nutrient and the inverse of total energy, when the total calorie intake is associated with the outcome, dividing by total calories might change the direction of association between the nutrient and outcome (Willett et al., 1997). Despite these methodological limitations, ISMs provide diverse approaches for researchers to investigate nutrient and food variables.

The current study also has limitations, including FFQ measurement, cross-sectional design, and the sample. First, regarding FFQ, Neuhouser et al. (2008) and Prentice et al. (2011) have confirmed the existence of systematic bias in dietary self-reports and provide methods of correcting for measurement error. Specifically, participant characteristics predicted misreporting, for example, younger women had more underreporting of energy and protein; those with higher BMI underreporting of energy; Blacks and Hispanics underreported more than did Caucasians (Neuhouser et al., 2008; Prentice et al., 2011). However, because the FFQ was updated from the original WHI FFQ to reflect the changing food supply, calibration equations developed within the WHI main study to account for measurement errors were not applied. Further, because an FFQ is composed of a pre-specified food list, it may not reflect the eating patterns of any given population. Second, the exemplar we illustrated from WHI data is cross-sectional in design, but substitution can also be adopted in other designs, such as clinical trials and other longitudinal studies with logistic regression or Cox regression. Third, the sample studied here was limited to older women, so the generalizability of the current finding is limited. In addition, a post hoc power analysis showed within this sample size the power to detect the calculated effect size was

relatively low (0.64-0.79 in macronutrient analysis and 0.94-0.96 in food analysis), so the results for the density model might be affected due to the low power. Finally, due to the limited space, the paper provides a brief introduction of categorical nutrients, and more details can be found in other papers (Brown et al., 1994; Hu et al., 1999).

### **Conclusions**

Researchers in nursing can benefit from using isocaloric substitution methods. To sum up, a partition method can be used to study both food and nutrients but usually serves as a supplementary analysis rather than the main analysis. A standard multivariate method can be used to study both food and nutrients; although collinearity may appear between total energy and individual nutrients, collinearity is usually not considered a concern. A residual method can be used to study both food and nutrients, but this method is not a choice when zero intakes are reasonable. A density method usually is used to study nutrients, but when total energy intake is a strong predictor of the outcome, the interpretation should be carefully examined and maybe a residual method is more appropriate. Compared with other methods, the density method is more appropriate when individuals are of varied body sizes. To simplify, the best choice of method for food analysis is a standard multivariate method and for nutrient analysis is a residual method or density method. We expect that this real data example will serve as a road map that will help researchers in nursing understand the strengths and limitations of the ISMs approach. The improved understanding may, in turn, facilitate collaborations with nutrition scientists and statisticians concerning available methods to study nutrition. This aligns with the NIH 2020-2030 strategic plan that new collaborations across institutes, such as NINR, NIDDK, and NCCIH, to promote nutrition research is needed.

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**Table 3.1** Baseline Characteristics by Overall Fatigue Score Quartiles for 4563 Women’s Health Initiative Participants age 65 and older

Variable	Total participants (n=4563)
Age (mean ± SD)	78.99± 6.6
<b>Education, n (%)</b>	
High school or less	902(20)
Some college	1772(39)
College or more	1889(41)
<b>Ethnicity, n (%)</b>	
White	2440(53)
Black	1350(30)
Hispanic	773(17)
NSES (mean ± SD)	73.46±9.37
Social Support* (mean ± SD)	37.34±7.5
<b>Sleeping hours, n (%)</b>	
<= 7 hours	1444(32)
8~9 hours	1979(43)
>= 10 hours	1140(25)
Diabetes, n (%)	866(19)
BMI, mean ± SD	27.95±5.64
Depression, n (%)	259(5.7)
Number of Chronic Diseases (mean ± SD)	0.95±0.83
<b>Self-Rated Health, n (%)</b>	
Excellent/very good	2371(52)
Good	1776(39)
Fair/poor	416(9)
<b>Physical Activity</b>	
LLPA, min/d (mean ± SD)	188.84±49.39
HLLPA, min/d (mean ± SD)	99.17±35.19
MVPA, min/d (mean ± SD)	51.83±34.68
<b>Nutrition Variables from FFQ</b>	
Nuts, Oz equivalents of lean meat (mean ± SD)	0.94±1.07
Legumes, Oz equivalents of lean meat (mean ± SD)	0.4±0.6
Egg, Oz equivalents of lean meat (mean ± SD)	0.37±0.48
Fish, Oz cooked lean meat (mean ± SD)	0.74±0.78
Poultry, Oz cooked lean meat (mean ± SD)	0.84±0.74
Red and processed meat, Oz cooked lean meat (mean ± SD)	1.61±1.4
Protein Foods Group, Oz Equivalent (mean ± SD)	4.9±2.64
Energy, kcal/day (mean ± SD)	1607.53±646.7
Protein, gram/day (mean ± SD)	64.44±27.95
Vegetable protein, gram/day (mean ± SD)	22.81±10.73
Animal protein, gram/day (mean ± SD)	41.63±21.61
Alcohol, gram/day (mean ± SD)	5.39±11.71
Carbohydrate, gram/day (mean ± SD)	203.06±86.63
Fat, gram/day (mean ± SD)	55.53±27.03

*Note.* NSES: Neighborhood Social Economic Status. BMI: Body Mass Index; LLPA: low light physical activity; HLLPA: high light physical activity; MVPA: moderate to vigorous physical activity. \*Social support total score spanned from 9 to 45.

**Table 3.2** Energy Adjustment Method and Model Composition Analyzing Protein Foods and Fatigue Association (n=4563)

<b>Models</b>	<b>Model composition</b>
Conventional regression method	Fatigue = Fish + poultry + nuts + legumes + egg + red and processed meat
Partition method	Fatigue = Fish + poultry + nuts + legumes + egg + red and processed meat + total energy intake
Standard multivariate method	Fatigue = Fish + poultry + nuts + legumes + egg + total protein + total energy intake
Residual method	Fatigue = RFish + RPoultry + RNuts + RLegumes + REgg + total protein + total energy intake

*Note:*

- a. adjusted for age, ethnicity, education, Neighborhood Socioeconomic Status (NSES), self-rated health, depression, BMI, number of chronic diseases, sleeping hours, social support, diabetes, low light physical activity time, high light physical activity time, moderate to vigorous physical activity time.
- b. Each food variable is in the unit of oz equivalent, and total energy intake is in the unit of kcal.
- c. Rfish refers to the residual of the model in which each food group is regressed on total protein foods.

**Table 3.3** Energy Adjustment Methods Analyzing Protein Foods and Fatigue Association (n=4563)

<b>Models</b>	<b>Variables of each model</b>					
Conventional method	Fish 1.10(0.46,1.73) *	Poultry -1.2(-1.88, -0.53) *	Nuts 0.24(-0.21, 0.68)	Legumes 0.81(0, 1.61)	Egg -0.9(-1.94, 0.11)	Red & processed meat -0.62(-0.97, -0.26) *
Partition method	Fish 1.27(0.62, 1.93) *	Poultry -1.04(-1.77, -0.31) *	Nuts 0.44(-0.04, 0.92)	Legumes 1.13(0.23, 2.03) *	Egg -0.81(-1.83, 0.22)	Red & processed meat -0.41(-0.81, -0.01) *
Standard method	Fish 1.68(0.97, 2.40) *	Poultry -0.63(-1.47, 0.21)	Nuts 0.85(0.27, 1.42) *	Legumes 1.54(0.60, 2.48) *	Egg -0.4(-1.54, 0.75)	Total protein food -0.41(-0.81, -0.01) *
Residual method	RFish 1.68(0.97, 2.40) *	RPoultry -0.63(-1.47, 0.21)	RNuts 0.85(0.27, 1.42)*	RLegumes 1.54(0.60, 2.48) *	REgg -0.4(-1.54, 0.75)	Total protein food 0.01(-0.24, 0.26)

*Note:*

- a. adjusted for age, ethnicity, education, Neighborhood Socioeconomic Status (NSES), self-rated health, depression, BMI, number of chronic diseases, sleeping hours, social support, diabetes, low light physical activity time, high light physical activity time, moderate to vigorous physical activity time, total energy intake
- b. Each food variable is in the unit of oz equivalent, and total energy intake is in the unit of kcal.
- c. Rfish refers to the residual of the model in which each food group is regressed on total protein foods.

**Table 3.4** Multivariate Density Model Among Macronutrients (n=4563)

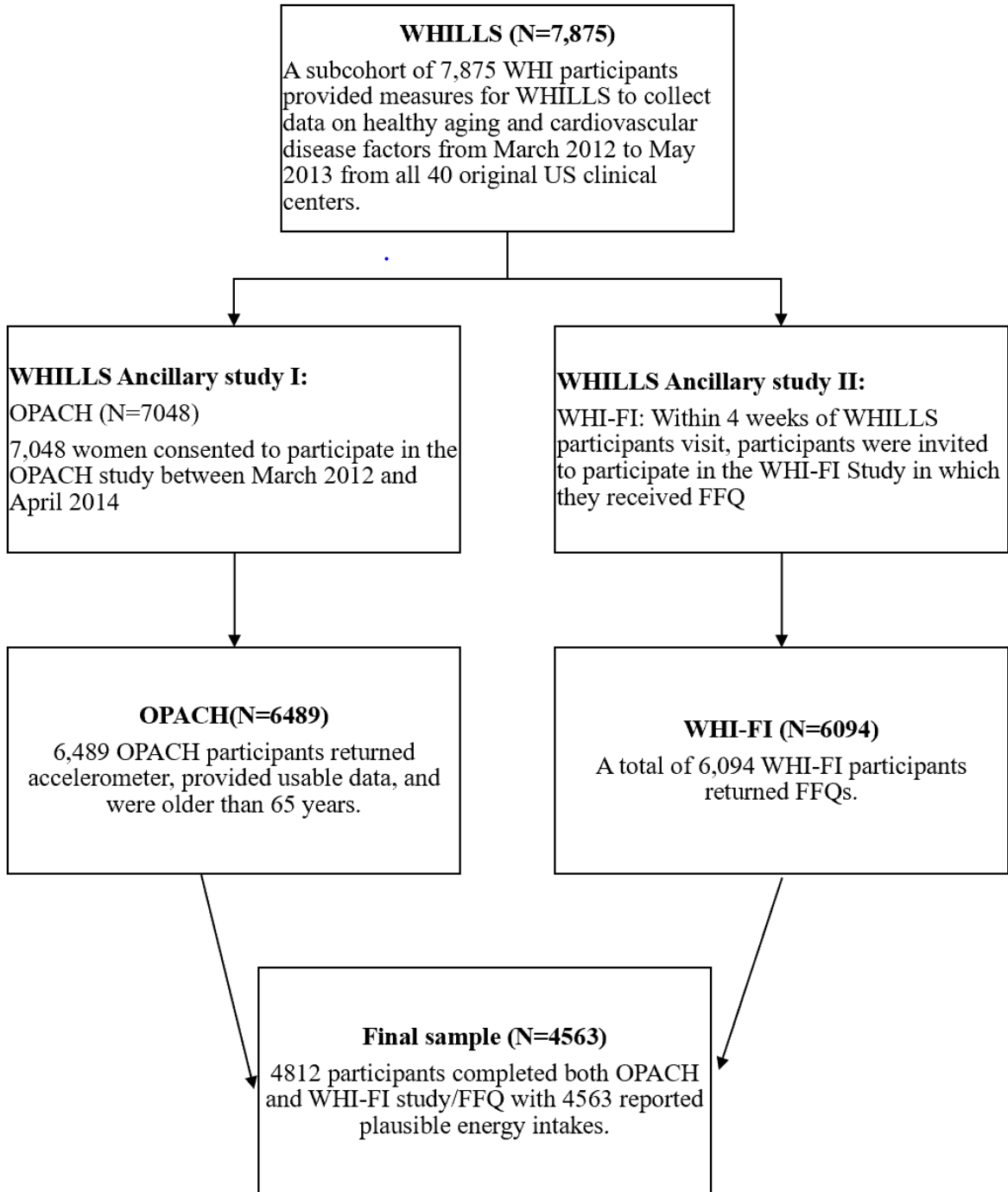
<b>Models</b>	Vegetable Protein substitute for animal protein	Fat substitute for animal protein	Carbohydrate substitute for animal protein	Alcohol substitute for animal protein	Total energy
Multivariate Density Model	2.40 (0.86, 3.94) *	-1.11(-1.95, -0.27) *	-0.62(-1.36, 0.12)	-0.47(-1.31, 0.37)	0(0, 0) *

*Note:*

a. adjusted for age, ethnicity, education, Neighborhood Socioeconomic Status (NSES), self-rated health, depression, BMI, number of chronic diseases, sleeping hours, social support, diabetes, low light physical activity time, high light physical activity time, moderate to vigorous physical activity time.

b. Each nutrient variable and total energy intake are in the unit of kcal.

**Figure 3.1** Flowchart of final analytical sample



**Supplementary Table 3.1** Correlations among food groups, total energy intake, total protein foods, and fatigue

Variables	1	2	3	4	5	6	7	8	9
1 Fatigue	1								
2 Red and processed meat	-0.11***	1							
3 Fish	0.06***	0.03**	1						
4 Poultry	-0.04**	0.18***	0.24***	1					
5 Nuts	0.05**	0.05***	0.08***	0.08***	1				
6 Legumes	0.04**	0.01	0.15***	0.05***	0.11***	1			
7 Eggs	-0.05***	0.21***	0.13***	0.13***	0.04**	0.07***	1		
8 Total energy intakes	-0.07***	0.50***	0.29***	0.34***	0.37***	0.30***	0.25***	1	
9 Total protein foods	-0.03	0.66***	0.47***	0.52***	0.52***	0.36***	0.40***	0.71***	1

Note. \* indicated  $p < .05$ ; \*\* indicates  $p < .01$ ; \*\*\* indicates  $p < .001$

**Supplementary Table 3.2** Correlations among nutrient variables, nutrient density variables, total energy intake, total protein foods, and fatigue

Variables	1	2	3	4	5	6	7	8	9	10	11
1 Fatigue	1										
2 Total Energy Intakes	-	1									
3 Total Protein foods	0.07****		1								
4 Alcohol Density	-0.03	0.71***		1							
5 Carbo Density	0.07****	0	-0.03*		1						
6 Protein Density	0.03	-0.07****	-	-		1					
7 Fat Density			0.43****	0.38****			1				
8 Protein	0.02	-0.07****	0.39****	-	-	0.16****	0.36****				
9 Carbohydrate	-	0.12****	0.35****	-	-	0.18****	0.76****	0.08****	1		
10 Fat	0.09****			0.07****	0.21****			0.38****	0.13****	1	
11 Alcohol	-	0.88****	0.84****	-	-	0.29****	-	-	0.75****	1	
	0.05****			0.14****		0.19****	0.16****				1
	-	0.88****	0.76****	-	-	-0.03	0.53****	0.79****	0.68****		
	0.10****			0.09****	0.38****						
	0.06****	0.17****	0.09****	0.92****	-	-	-	0.07****	0.01	0.05****	1
					0.35****	0.16****	0.16****				

Note. \* indicated  $p < .05$ ; \*\* indicates  $p < .01$ ; \*\*\* indicates  $p < .001$

**Chapter 4. Mediterranean diet and fatigue among community-dwelling postmenopausal women**

### **Abstract**

We investigated cross-sectional relationships between the Mediterranean diet and overall fatigue, energy, and weariness scores among 4563 women aged 65+ from the Women's Health Initiative study. We also used the Isocaloric Substitution approach to explore whether the substitution of fish for red and processed meat, whole grains for non-whole grains, and whole fruit for fruit juice relate to RAND-36 measured overall fatigue and its subdomains. The alternate Mediterranean Diet (aMED) Index quintiles (Q1-Q5) and selected Mediterranean foods available on a Food Frequency Questionnaire were exposure measures. Results showed aMED Q5 was associated with 2.99 (95% CI: 0.88, 5.11), 4.01 (95% CI: 1.51, 6.53), and 2.47 (95% CI: 0.24, 4.70) point improvements in fatigue, energy, and weariness scores, respectively, compared with aMED Q1. Substituting fish for red and processed meat and whole for non-whole grains was associated with more favorable fatigue scores, whereas substituting whole fruit for juice was not.

(word count: 148)

*Keywords:* Mediterranean diet, fatigue, older women

## **Introduction**

Fatigue, the subjective report of weariness and lack of energy, is a common and bothersome symptom in older adults. Estimates show that about 27% to 50% of community-dwelling adults 65 years and older and 75% of adults 85 and older report fatigue,<sup>1</sup> and studies showed fatigue is more prevalent among older women than older men.<sup>2,3</sup> In older adults, fatigue significantly relates to a decreased function and performance, including physical,<sup>4,5</sup> cognitive functioning,<sup>6</sup> and specific task performance such as chair rise.<sup>7</sup> Studies also found about twice the risk of hospitalization and using home help five years later<sup>8</sup> and a higher risk of mortality among fatigued older adults than unfatigued older adults.<sup>4,9</sup> Besides, for fatigued older individuals, decreased functioning leads to an increased need for further effort, and thus, fatigue worsens. This spiral helps to explain the unremitting nature and escalation of fatigue.<sup>10</sup> A need to address unfolding escalation in fatigue in a rapidly growing number of older adults led to a concerted effort by researchers to understand modifiable factors that prevent fatigue and improve outcomes in those who experience fatigue. Nutritional factors are especially pertinent in that regard because they are modifiable and have been implicated in experiments and randomized clinical trials (RCTs) in fatigue occurrence and severity.<sup>11,12,13</sup> Despite the promising findings that involve individual nutrients, the role of the dietary pattern has yet to be examined in relation to fatigue, especially while leveraging well-powered cohorts with characterized dietary measures. Dietary patterns represent an integrated picture of frequency, proportion, and variety of food, drinks, and nutrient consumption in a habitual diet.<sup>14</sup> Compared with individual nutrients, dietary patterns are more advantageous for research and clinical use because they consider the substitution effect and synergic and antagonistic interactions between nutrients.<sup>15</sup>

### **RCTs and Epidemiological Evidence**

Although many dietary patterns exist, the Mediterranean diet – a way of eating based on

the traditional cuisine of Mediterranean countries and typically high in vegetables, fruits, whole grains, fish, beans, nuts and seeds, and olive oil – might be relevant to studying fatigue in old age as the diet has been studied in people aged 65 years and older.<sup>16–20</sup> These studies, however, were limited by ad hoc measures of fatigue, which were commonly operationalized as one or two items from the Center for Epidemiologic Studies Depression Scale (CES-D) scale.<sup>18–20</sup> Some RCTs were identified, which showed adhering to a Mediterranean diet significantly improved fatigue.<sup>21–22</sup> Although informative, one important caveat is that all these previous studies were focused on clinical populations (e.g., people with diabetes or people with arthritis) and missed the opportunity to examine the dietary pattern-fatigue relationship among a more general population of community-dwelling older adults. Further, most studies examining the Mediterranean diet and fatigue relationship considered only the role of nutrition, but not physical activity.<sup>18–20</sup> Individuals who adhere to a healthy diet are commonly engaged in other healthy behaviors such as physical activity, and physical activity relates to fatigue;<sup>23</sup> as such, it is crucial to include physical activity in the model to adjust for the potentially confounding relationship.

### **Potential Physiological Mechanisms of the Mediterranean Diet Related to Fatigue**

The exact mechanism by which a Mediterranean diet exerts its beneficial effects in improving fatigue is not known. A Mediterranean-style diet might influence fatigue through the pathways of reduced saturated fatty acid intake, reduced amino acid, reduced calorie intake, increased phytochemical intake, and gut microbiota.<sup>24</sup> For people with high adiposity, the Mediterranean diet might not only affect fatigue via anti-inflammation and anti-oxidation but also trigger other metabolic pathways involved in lipid processing.<sup>24</sup> Thus, the association between the Mediterranean diet and fatigue might differ among those with high versus low adiposity. Similarly, fatigue is a common symptom in people with diabetes,<sup>25</sup> and as the

Mediterranean diet has been involved in insulin regulation,<sup>24</sup> there might be an additional benefit for those with diabetes compared with those without diabetes.

### **Isocaloric Substitution Method (ISM)**

Beyond the association and interaction analysis in examining dietary patterns and fatigue, an increasing number of studies have started using isocaloric substitution methods (ISM) to compare the relative health contributions of different foods and macronutrients.<sup>26–30</sup> ISM is, in nature, a linear regression.<sup>31,32</sup> Substitution is achieved via including both the nutrients of interest and the total energy intake as independent variables. As such, the interpretation of each coefficient of individual food group/macronutrient refers to the change in outcome when substituting the food group/macronutrient for the food group/macronutrient excluded in the model. The application of ISM removes confounding effects from total energy intake, reduces extraneous variation, and predicts or mimics the effect of dietary interventions.<sup>31</sup> ISM is relevant to study dietary patterns in general and the Mediterranean diet in particular because the health impact of a specific food item cannot be isolated from that of other foods it replaces; further, individuals usually alter the intake of specific foods primarily by changing the dietary composition rather than by changing the total energy intake unless physical activity or body composition change considerably.<sup>31</sup> Since the Mediterranean diet includes a high intake of vegetables, fruits, fish, and whole-grain and a relatively low intake of red and processed meat and non-whole grains; it is, therefore, important to examine how substituting certain favorable for unfavorable foods under the same food category relates to fatigue. Furthermore, the Mediterranean diet recommends a high intake of fruits; however, it is still unclear whether both whole fruits and fruit juices confer similar health benefits concerning fatigue. Some researchers considered juice as a mere source of sugar,<sup>33</sup> which might increase hypertension risks,<sup>34</sup> but

others suggested that fruit juice is a good source of vitamin C, folate, potassium, and polyphenols.<sup>35</sup>

In this study, we examined three questions. 1) Is there an association between the Mediterranean diet and fatigue among community-dwelling older women while adjusting for physical activity and relevant confounders? 2) To what extent do diabetes and body mass index (BMI) individually moderate the relationship between the Mediterranean diet and fatigue, adjusting for physical activity and relevant confounders? 3) Does the substitution of fish for red and processed meat, whole grain for refined grain, and whole fruit for fruit juice relate to improved fatigue separately, adjusting for physical activity and relevant confounders? We hypothesized that higher adherence to the Mediterranean diet would be associated with an improvement in the scores of fatigue and its subdomains in community-dwelling older women; diabetes and BMI would individually moderate the relationship between the Mediterranean diet and fatigue; and the substitution of fish for red and processed meat, whole grain for refined grain, and whole fruit for fruit juice would relate to improved fatigue separately.

## **Methods**

### **Sample**

The study is an observational cross-sectional design with participants from two ancillary studies of the Women's Health Initiative Long Life Study (WHILLS): Objective Physical Activity and Cardiovascular Disease Health (OPACH) Study and WHI-Food Intake (WHI-FI). Details about the main WHI study have been previously described.<sup>36</sup> The WHILLS was conducted to collect data on healthy aging and cardiovascular risk factors during the second Extension Study of the WHI among a subcohort of 7,875 WHI participants from March 2012 to May 2013 from all 40 original US clinical centers.<sup>37</sup> Among WHILLS, 7,048 women consented to participate in the OPACH study, and they were provided with an ActiGraph GT3X+

(Pensacola, Florida) triaxial accelerometer, a sleep log, and an OPACH Physical Activity (PA) Questionnaire between March 2012 and April 2014 either during a home visit or via express mail afterward. Participants were asked to wear the triaxial accelerometer on their hip for seven consecutive days during waking and sleeping hours except when bathing or swimming.<sup>38</sup> The WHI-FI ancillary study also recruited participants from WHILLS. Within four weeks of completing WHILLS measures, WHILLS participants received an invitation to participate in the WHI-FI Study in which they received a Food Frequency Questionnaire (FFQ).<sup>39</sup> A total of 6,094 FFQs were returned by WHILLS participants. For this current study, we retained 6,489 OPACH participants who returned their accelerometer, provided usable data, and were older than 65 years. Among the 6,489 women, 4,812 completed FFQs and 4,563 reported plausible average energy intakes, defined as  $\geq 600$  kcal and  $\leq 5,000$  kcal.<sup>40</sup> These 4,563 women composed our final analytical sample (see **Figure 4.1**). Approval was obtained from the Fred Hutchinson Cancer Research Center Institutional Review Board as well as from each clinical center's Institutional Review Board, and all WHI participants provided written informed consent.

## Measures

**Dietary variables.** Diet was measured at WHILLS baseline via FFQ. The FFQ included 140 composite and single-food line items asking about frequencies and approximate portion sizes consumed during the past three months, among which thirteen adjustment questions asked about fat intake, fortification of juices consumed, and type of cold cereal consumed. Three summary questions asked about the usual intake of fruits, vegetables, and added fats for comparison with information gathered from the line items. Nutrient calculations based on reported intake were performed using the Nutrition Data System for Research software version 2012, developed by the University of Minnesota Nutrition Coordinating Center.<sup>41</sup> Total energy intake was calculated

as:  $4 \text{ (kcal/ gram)* carbohydrate (gram/day)} + 4 \text{ (kcal/ gram)* protein (gram/day)} + 9 \text{ (kcal/ gram)* fat (gram/day)} + 7 \text{ (kcal/ gram)* alcohol (gram/day)}$ .<sup>26</sup>

The food groups involved in the substitution analysis are as follows. Fish intake included fried fish, fish sandwich, fried shellfish, not fried shellfish (i.e., shrimp, lobster, crab, and oysters), canned tuna, tuna salad, tuna casserole, broiled or baked white fish, and broiled or baked dark fish (i.e., salmon, mackerel, bluefish). Red and processed meat included frankfurters, sausage, processed, luncheon meats, cooked lean meat from all types of organ meats, including that from beef, pork, veal, lamb, game, poultry, and fish. Whole grain options included whole-grain bread and rolls, whole grain crackers, whole grains as a side dish such as brown rice, and whole-wheat pasta. The following fruit items were included as whole fruits: apples, applesauce, peaches, nectarines, pears, bananas, plums, apricots (fresh, canned, or dried); oranges, grapefruit, and tangerines (not juice); cantaloupe, orange melon, and mango, watermelon and red melon; berries such as strawberries and blueberries; dried fruit (other than apricots) such as raisins and prunes; any other fruit such as grapes, fruit cocktail, pineapple, and cherries. Fruit juice was composed of two separate items asking about orange and grapefruit juices and all other 100% fruit juice types.<sup>42</sup>

**The alternate Mediterranean diet (aMED) score.** Based on nutrient and food item intakes estimated from the FFQ, an aMED index was used to assess the extent of adherence to a Mediterranean Diet. The aMED score was adapted from a traditional Mediterranean diet to accommodate for use among people in non-Mediterranean countries.<sup>43</sup> The aMed index has nine components: whole grains, vegetables (excluding potatoes), fruits (including juices), legumes, nuts, fish, ratio of monounsaturated fat to saturated fat, red and processed meats, and alcohol.<sup>43,44</sup> For fruits, vegetables, nuts, legumes, whole grains, fish, or ratio of monounsaturated to saturated

fat, when intake was above the median of each component, participants received one point. For red and processed meat, when consumption was below the median, one point was counted. For alcohol, the participant received one point only when the intake was between 5 and 15 g/d. Otherwise, participants received zero points. The total aMED index score spans from 0 (minimal adherence to the diet) to 9 (maximal adherence to the diet).

**Fatigue measurement.** The RAND-36 Vitality subscale<sup>45</sup> was used to measure overall fatigue and its two subdomains: energy and weariness. The Vitality subscale comprises four questions that ask about the frequency of having a lot of energy and feeling tired, worn out, and full of pep over the previous four weeks, with item responses ranging from 1 (all the time) to 6 (none of the time). Energy was calculated as the mean of feeling full of pep and having a lot of energy; weariness was calculated as the mean of feeling worn out and feeling tired; and overall fatigue was calculated as the mean score of the four questions. Overall fatigue, energy, and weariness were then recoded to range from 0 to 100, with a higher score representing a more favorable health status.<sup>45–48</sup>

**Accelerometer measurement.** Accelerometer data from the three planes (i.e., vertical plane and the two other axes) were processed using ActiLife software version 6 (Pensacola, FL) using 15-second epochs and the normal filter and then integrated with a vector magnitude, an indicator of total physical activity volume. The criteria for physical activity classification were low light-intensity physical activity (LLPA, 19–225 counts/15 s), high light-intensity physical activity (HLLPA, 226–518 counts/15 s), and moderate to vigorous physical activity (MVPA,  $\geq 519$  counts/15 s).<sup>49</sup>

**Body Mass Index (BMI) and Diabetes.** BMI and diabetes served as moderator variables. BMI was collected during the home visit by self-report of weight and height and

calculated by dividing the weight (kg) by the square of the height (m). BMI was categorized as underweight ( $\leq 18.5$ ), normal weight (18.5–25), overweight/obese ( $\geq 25$ ). Diabetes was measured by a self-report question “Has a doctor ever told you that you had sugar diabetes or high blood sugar when you were not pregnant?” Self-reported diabetes has correctly classified diabetes cases and non-cases and is sufficiently accurate to allow use in epidemiologic studies.<sup>50,51</sup>

**Covariates.** The list of covariates included demographics (age, race/ethnicity, education, Neighborhood Social Economic Status [NSES]), health-related variables (self-rated health, depression, diabetes, BMI, number of chronic diseases), and health behavior variables (sleeping hours, social support, low light physical activity time, high light physical activity time, moderate to vigorous physical activity time, total energy). Depression was measured via a shortened version of the Center for Epidemiological Studies Depression Scale (CES-D) and considered a score greater or equal to 0.06 as evidence of depressive symptoms.<sup>52</sup> The number of self-reported chronic diseases was measured as the sum of chronic obstructive pulmonary disease, cardiovascular disease, cerebrovascular disease, cancer, osteoarthritis, and cognitive impairment. To evaluate social support, a questionnaire from the Medical Outcomes Study (MOS) was included. The questionnaire was designed to assess the amount of social support the patient has available, including nine questions (four subscales: emotional/informal support, affection, tangible support, and positive social interaction) about how often each different type of support is available to participants. Responses were scored on a five-point scale ranging from “none of the time” to “all of the time.”<sup>53</sup> Sleeping time variable was taken from OPACH Form 321, and it referred to the number of hours spent sleeping during a usual day and night. Responses ranged from 1= $\leq$ 4 hours to 8=16+ hours. Race/ethnicity and the highest level of education were from the WHI baseline (1993–1998). Age, self-rated health, depression, and the number of chronic

diseases were from WHI or LLS questionnaires proximal to the OPACH study baseline. Data from the 2000 census were used to assess NSES at the census tract level. NSES was an index of the six census tract variables: (1) percent of those older than 25 with the education less than high school; (2) percent of male unemployment; (3) percent of households whose income are below the poverty line; (4) percent of households receiving public assistance; (5) percentage of female-headed households with children; and (6) the median household income. The variables for the index were identified through confirmatory factor analysis. This NSES index was shown from prior studies as a crucial neighborhood-level predictor of a variety of health outcomes.<sup>54-56</sup> The NSES index was considered a continuous variable ranging from 0 to 100 for US census tracts; higher scores indicated more affluent tracts.

### **Missing Data**

The primary missingness came from the outcome variable fatigue (missing rate: 7.2%) and covariates which mainly included NSES (missing rate: 10.7%), social support (missing rate: 9.6%), depression (missing rate: 9%), sleep (missing rate: 3.4%), and BMI (missing rate: 0.7%). The exposure variables had almost no missingness as we chose people with plausible nutritional data in analysis as depicted in Figure 1. We conducted multiple imputations based on the maximizing expectation method to account for the missing data in both dependent and independent variables.<sup>57</sup> A list of food groups and nutrients was excluded in our analytical model but served as auxiliary variables to generate our ten imputed datasets, thus optimizing the approximation. Models were run on each of the 10 imputed datasets, and then parameter estimates and variances were calculated, based on Rubin's rule.<sup>58,59</sup>

### **Statistical Analysis**

First, we ran descriptive analytics for demographic and health characteristics in the imputed dataset by four quartiles of overall fatigue scores. Comparison of the variables across outcome quartiles was conducted by Chi-square test for categorical variables, ANOVA for continuous variables, and Kruskal-Wallis tests for non-normally continuous variables. Next, multiple linear regression models were conducted with aMED quintiles as predictor variables (i.e., Quintile 1= aMED ranged between [0, 2); Quintile 2 = [2, 4); Quintile 3 = [4, 5), Quintile 4 = [5, 6); Quintile 5 = [6, 9]) and overall fatigue/energy/weariness as dependent variables. A list of covariates was selected based on previously established knowledge of factors relating to fatigue and Bayesian model averaging (BMA), an application of Bayesian inference to model selection. Then, the cross-product terms of aMED levels and BMI levels (aMED Quintile 1& overweight/obese as the reference group) and aMED levels and diabetes (aMED Quintile 1& without diabetes as the reference group) were added to the regression models to explore whether the relationship of aMED on fatigue depended on body size and diabetes. Isocaloric substitution models were estimated to quantify the trade-off in substituting fish for red and processed meat, whole grain for non-whole grain, and whole fruit for fruit juices while adjusting for all covariates, the total energy intake, and all other energy sources. Fish and red and processed meat were in the unit of ounces of cooked lean meat; grains were in the unit of ounce equivalents, fruits and juice were in the unit of cup equivalents. The *p* values for statistical tests were 2 tailed and considered statistically significant at an alpha level of 0.05. All analyses were performed with RStudio (version 3.6.2).

## Results

The demographic and nutrition characteristics of the analytical sample are shown in **Table 4.1**. As shown, the average age (SD) was 78.99 (6.6) and 53% were White. The number of older women in underweight, normal weight, and overweight/obese categories were 67, 1482,

and 3014, respectively. The average (SD) aMED score was 4.24 (1.87), and the average daily intake of whole grains, fruits, and vegetable consumption for the overall participants was 1.54 ounce equivalents, 1.53 cups, and 1.49 cups, respectively. Participants with more favorable fatigue scores were healthier (Quartile 1: 25% self-reported excellent health; Quartile 4: 80% self-reported excellent health), leaner (Quartile 1: BMI of 29.03; Quartile 4: BMI of 26.81), and more active (Quartile 1: MVPA of 40.38 min; Quartile 4: MVPA of 65.06 min); and fewer reported sleep for more than 10 hours (Quartile 1: 34% sleep  $\geq$  10 hours; Quartile 4: 17% sleep  $\geq$  10 hours,  $p < .001$ ). Participants with more favorable fatigue scores reported similar intakes of fruits (Quartile 1: 1.48 cup equivalents; Quartile 4: 1.59 cup equivalents,  $p = .075$ ) but tended to have a higher intake of vegetables (Quartile 1: 1.37 cup equivalents; Quartile 4: 1.62 cup equivalents,  $p < .001$ ) while having less intake of total energy (Quartile 1: 1645.6 kcal/day; Quartile 4: 1528.45 kcal/day,  $p < .001$ ), red and processed meat (Quartile 1: 1.77 ounce; Quartile 4: 1.36 ounce,  $p < .001$ ), fat (Quartile 1: 58.2 gram/day; Quartile 4: 51.12 gram/day,  $p < .001$ ), carbohydrate (Quartile 1: 207.2 gram/day; Quartile 4: 194.12 gram/day,  $p < .001$ ), and animal protein (Quartile 1: 42.82 gram/day; Quartile 4: 38.86 gram/day,  $p < .001$ ).

Regression models showed that Quintile 5 (i.e., aMED score ranging between [6, 9]) was favorably associated with overall fatigue and energy in minimally, partially, and fully adjusted models, compared with aMED Quintile 1 (**Table 4.2**). As shown, after controlling for various levels of physical activities, the magnitude of Quintile 5 coefficient slightly diminished; however, it was significantly associated with a 2.99 (95%CI: 0.88, 5.11) improvement in overall fatigue score, 4.01 (95%CI: 1.51, 6.53) improvement in energy score, and 2.47 (95%CI: 0.24, 4.70) improvement in weariness score, compared with aMED Quintile 1.

The interaction between aMED quintiles and BMI levels or aMED quintiles and diabetes

were non-significant for all three fatigue outcomes. For all three outcomes, the interaction showed underweight:aMED Q2,  $p > .05$ ; underweight:aMED Q3,  $p > .05$ ; underweight:aMED Q4,  $p > .05$ ; underweight:aMED Q5,  $p > .05$ ; normalweight: aMED Q2,  $p > .05$ ; normalweight: aMED Q3,  $p > .05$ ; normalweight: aMED Q4,  $p > .05$ ; normalweight: aMED Q5,  $p > .05$  & aMED Q2:Diabets,  $p > .05$ ; aMED Q3:Diabets,  $p > .05$ ; aMED Q4:Diabets,  $p > .05$ ; aMED Q5:Diabets,  $p > .05$ . For ease of interpretation, we simulated the adjusted mean values across the regression models with interaction terms. See **Supplementary Figure 4.1**.

**Figure 4.2** showed that regressions estimates, namely the mean score change in overall fatigue, energy, and weariness from substituting one-ounce fish for the same number of ounces of red and processed meat were 1.69 (95% CI: 0.99, 2.39), 2.22 (95% CI: 1.36, 3.07), and 1.11 (95% CI: 0.34, 1.88) points on overall fatigue, energy, and weariness scores. Of note, one ounce red and processed meat represented 62% of red and processed meat that WHI participants consumed on average; one ounce equivalent of fish approximated 135% of average daily consumption of fish in the WHI data. The regressions estimates, namely the mean score change in overall fatigue, energy, and weariness from substituting one-ounce equivalents of whole grain for the same amount of non-whole grain were 0.68 (95% CI: 0.20, 1.16) and 0.90 (95% CI: 0.39, 1.4) points in overall fatigue and weariness scores, respectively. One-ounce equivalents represented approximately 37% of non-whole grain and 65% of whole-grain consumption for WHI participants per day on average. The regressions estimates from the substituting of one-cup equivalents of whole fruit for the same amount of fruit juice were not significant. The regression estimates were 0.2, (95% CI: -0.66, 1.06), 0.28 (95% CI: -0.78, 1.35), and 0.14 (95% CI: -0.75, 1.02) for overall fatigue, energy, and weariness, respectively.

## Discussion

This paper described the associations between the Mediterranean diet and overall fatigue/energy/weariness in a general population of women aged 65 years and older. The mean aMED score of those older women was 4.24 (1.87) on a range between 0 and 9, similar to the score of 4.3 reported in a previously published WHI study of a younger (mean age = 64) but larger cohort (sample size > 90000).<sup>60</sup> The aMED score of 4.3 out of 9 indicated a moderate adherence to the Mediterranean diet among community-dwelling older women. Due to a lack of aMED classification, the moderate category was based on traditional Mediterranean diet scores,<sup>44,61</sup> whose tertile classification was similar for tertiles of aMED across samples.<sup>62</sup> Meanwhile, the average daily consumption of 1.53 cups, 1.49 cups, and 1.54 ounce equivalent of fruits, vegetables, and whole grains, respectively, indicated a relatively low consumption. According to the Healthy Mediterranean-diet recommendation offered by 2020-2025 Dietary Guidelines for Americans, the recommended amount for vegetables, fruits, and whole-grain were 2.5 cups, 2.5 cups, and 3 ounces for a person who eats 2000 calories per day.<sup>63</sup> Due to the wide variability, a distribution analysis showed in the current sample only 16% met the fruit recommendation, 13% met the vegetable recommendation, and 10.5% met the whole grain recommendation.

After adjusting for physical activity levels, we found that the magnitude of the relationship between aMED and fatigue declined, but a higher adherence to the Mediterranean diet was still significantly associated with more favorable fatigue/energy/weariness scores, indicating the unique contribution of the Mediterranean diet in addressing fatigue. Our finding was similar to a previous prospective study among older women with type 2 diabetes, where the Mediterranean diet significantly reduced fatigue, but the associations were attenuated when leisure-time physical activity was considered.<sup>22</sup> In our previous work, we found the importance of moderate and vigorous physical activity in relation to fatigue/energy/weariness.<sup>64</sup> Specifically,

we found 34 minutes of moderate and vigorous physical activity was associated with a 1- to 2-point improvement in fatigue/energy/weariness outcomes. In the current work, we found that optimal adherence to a Mediterranean diet was related to 2.5 to 4 point improvement in fatigue/energy/weariness compared to the lowest adherence. As such, it might be reasonable to assume that the combination of physical activity and the Mediterranean diet will act synergistically in mitigating fatigue. This assertion echoes prior research that suggested diet and physical activity have complementary and interactive effects on many physiological parameters such as energy, lipid, glucose, and metabolic balance.<sup>65</sup> Noticeably, physical activity is part of the Mediterranean lifestyle and is consistently recommended with the Med diet pyramids.<sup>66</sup> Thus, based on our findings, adherence to the Mediterranean lifestyle might relate to better fatigue scores in older women.

A minimal clinically important difference is essential to detect the smallest difference in fatigue score that these older women perceive as beneficial/improved fatigue feeling.. Prior research showed for the SF-36 vitality subscale, the minimal clinical difference ranged from 7.3 to 11.3 for improvement.<sup>67</sup> However, these numbers were drawn from people with rheumatoid arthritis and systemic lupus erythematosus, which might not be relevant to generally healthy community-dwelling older women. Another study revealed an average change of 5-10 points in SF-36 vitality as the minimal clinically important difference to predict job loss, hospitalizations, and mortality.<sup>68</sup> The combined effect of physical activity and the Mediterranean diet may or may not yield a clinically important difference; however, these lifestyle modalities may be suggested as health recommendations for women complementary to other evidence-based treatments of fatigue.

Non-significant interactions indicated a consistent diet-fatigue relationship across BMI levels and diabetes status. The similar Mediterranean diet-fatigue relationship in women with high and low BMI and persons with and without diabetes may show that salutary effects of the Mediterranean diet on fatigue transcend several metabolic factors. That is to say, physiological processes by which the Mediterranean diet affects fatigue may work through the routes that are not involved in fat and glucose metabolism. Unfortunately, we did not find previous publications that support this assertion; as such, further research is needed.

The ISM showed that one ounce fish substituted for red and processed meat relates to about a 2-point improvement in fatigue/energy. One ounce is about 62% of the red and processed meat one participant consumed on average. After the one ounce substitution, the average daily consumption of fish is estimated at 1.74 ounce (12.18 ounce per week), which still lags behind the recommended by Dietary Guidelines for Americans 2020-2025 15 ounce target.<sup>63</sup> This result may be especially useful for people loyal to animal protein consumption. Both fish and red meat are from animal sources; however, fish has a higher level of omega-3 fatty acids, so the beneficial effect of fish over red and processed meat may lie in levels of omega-3 fatty acids. Previous studies suggested omega-3 fatty acids were related to the anti-inflammatory process and the occurrence of fatigue.<sup>69</sup> Future researchers may consider testing the mechanism of omega-3 fatty acids by checking if the magnitude of the association alters after including omega-3 fatty acids in the model. However, there are other dietary differences between the two forms of animal protein which might serve as the potential mechanism.

We observed small benefits to substituting whole grain for the same amount of non-whole grain. However, it is challenging to study the mechanism of the substitution benefit because whole grain and non-whole grain are markedly different.<sup>70</sup> For example, compared with

non-whole grain, whole-grain foods tend to be higher in phytochemicals, fiber, and some B vitamins.<sup>71</sup> Fiber and phytochemicals were reported to be related to fatigue improvement through the cholesterol-lowering effect, protection against oxidative stress, inflammation, and beneficial modifications in gut microbiome taxonomy and metabolites.<sup>24</sup> Thus, pending further research, one cautions interpretation might be that whole grains may be more appropriate in the context of fatigue than non-whole grains. Our findings from ISM (i.e., fish in replace for red and processed meat and whole-grain for non-whole grain) supported that the beneficial effect of the Mediterranean diet might not be due to the action of a single food but rather the accumulated or synergic impact of several featured foods from Mediterranean diet or the overall Mediterranean diet lifestyle.

Our finding that the impact on fatigue from the substitution of one-cup equivalent of whole fruit for the same amount of 100% fruit juice was not significant provided preliminary evidence that 100% juice is as healthy as whole fruits concerning fatigue in this population. Although, there is currently no description about the role of 100% fruit juice in the Mediterranean diet, our finding resonates with the general healthy eating recommendations by 2020 - 2025 Dietary Guidelines for Americans, where both whole fruits and 100% fruit juices are promoted.<sup>63</sup> Our finding also resonates with experts participating in a roundtable discussion who stated a lack of science-based reason to restrict access to 100% fruit juice in public health nutrition policy.<sup>35</sup> The expert panel also estimated that reducing access to 100% fruit juice could lead to some unintended consequences such as reduced daily fruit intake and increased consumption of sugar-sweetened beverages.<sup>35</sup>

The strengths of this study include dietary pattern rather than individual foods as main exposure variables, the use of the relatively novel ISMs to examine the reallocation of food and

dietary variables, the inclusion of physical activities, and finally the generalized older population. First, we adopted Mediterranean dietary pattern as our exposure variable, especially we used the aMED score, which was tailored for people in non-Mediterranean countries but was reliable and valid measure in assessing adherence to Mediterranean diet.<sup>43</sup> We were therefore able to assess an integrated picture of frequency, proportion, and variety of food, drinks, and consider the substitution effect, synergic and antagonistic interactions between foods and nutrients. Second, by applying ISM, we were able to examine calories allocation among various foods groups to achieve improved fatigue scores. ISM removes confounding effects from total energy intake and allows for the study of multiple food groups and also the macronutrient composition while holding total energy constant to identify a better dietary pattern,<sup>40</sup> thus ISM can serve as another method to triangulate results in instances when RCT is not available. Third, we controlled physical activities and were able to find that our conclusion about Mediterranean diet remained after adjusting for physical activities. Besides, our physical activities were accelerometer measured and were calibrated specifically for older women. These objective physical activities are more nuanced and reliable than self-reports. Finally, we examined the relationship between dietary variables and fatigue in community-dwelling older women rather than a specific clinical population, thus, our findings are relevant to the majority of older women.

The limitations of this study include the sample, measurements, and cross-sectional design. First, the sample studied here, while racially diverse, was limited to older women. Previous research, however, did find differences between men and women concerning the metabolic effects of the Mediterranean diet.<sup>72,73</sup> Second, prior researchers have confirmed the existence of systematic bias in dietary self-reports and provided methods of correcting for measurement error.<sup>74</sup> However, because the FFQ was updated from the original WHI FFQ to

reflect the changing food supply, calibration equations developed within the WHI to account for measurement errors were not applied. Further, because an FFQ is composed of a pre-specified food list, it may not reflect the eating patterns of any given population.<sup>75</sup> Third, the NSES was collected around the year 2000 census, so it might not be a reliable representative of the true NSES. Fourth, despite the possibility of examining a longitudinal relationship between the Mediterranean diet and fatigue using WHI data, the sparseness of collection interval and out-of-date information may not represent a contemporary diet pattern, thus limiting our choice of analysis to the cross-section. The ISMs in the cross-sectional study should not be considered equivalent to a RCT in which real behavior changes occur over time and cause future outcomes.

### **Conclusions**

We showed that the Mediterranean diet was uniquely associated with fatigue, even after controlling physical activity levels. The Mediterranean diet's beneficial effect on fatigue seems similar among people with or without diabetes and obesity. Substituting fish for red and processed meat and whole grains for non-whole grains was associated with improvements in overall fatigue, energy, and weariness scores. Similar substitution of fruit for fruit juice was not associated with fatigue. These findings indicate that Mediterranean diet might have the potential to break the escalation of fatigue. Future researchers may consider including energy-fatigue measures in RCTs of older adults in which increasing adherence to the Mediterranean diet and reducing fatigue are intervention targets so that improvements in fatigue can be directly tested.

## **Take away points**

- Higher adherence to Mediterranean diet was associated with 2.5-to-4-point improvements in fatigue, energy, and weariness scores, compared with the lowest adherence to Mediterranean diet.
- The Mediterranean diet was independently associated with more favorable self-reported fatigue scores, even after controlling health and lifestyle factors.
- Substituting fish for red and processed meat and whole grains for non-whole grains was associated with more favorable fatigue scores, whereas substituting whole fruit for juice was not.

## **Acknowledgements**

The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts 75N92021D00001, 75N92021D00002, 75N92021D00003, 75N92021D00004, 75N92021D00005.

WHI Acknowledgment Statement: <https://www.whi.org/doc/WHI-Investigator-Short-List.pdf>

Hester Mclaws Nursing Scholarship from the School of Nursing at the University of Washington was provided to Ms. Su to support her dissertation work.

Oleg Zaslavsky received support from the National Institute on Aging under Award Number K23AG059912

## **Disclosure statement**

No potential conflict of interest was reported by the author(s).

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**Table 4.1** Baseline characteristics by overall fatigue score quartiles for 4563 Women’s Health Initiative participants age 65 and older

<b>Variable</b>	<b>Quartile 1 (0, 50] (n=1319)</b>	<b>Quartile 2 (50, 65] (n=1290)</b>	<b>Quartile 3 (65,75] (n=883)</b>	<b>Quartile 4 (75, 100] (n=1071)</b>	<b>Total participants (n=4563)</b>	<i>p</i> for Comparison
Age (mean ± SD)	79.85±6.73	79.61±6.41	78.69±6.52	77.45±6.38	78.99± 6.6	<i>p</i> <.001
<b>Education, n (%)</b>						<i>p</i> <.001
High school or less	293(22)	269(21)	163(18)	178(17)	902(20)	
Some college	564(43)	487(38)	329(37)	392(37)	1772(39)	
College or more	462(35)	534(41)	391(44)	501(47)	1889(41)	
<b>Race/Ethnicity, n (%)</b>						<i>p</i> <.001
White	771(58)	705(55)	464(53)	500(47)	2440(53)	
Black	360(27)	378(29)	267(30)	345(32)	1350(30)	
Hispanic	188(14)	207(16)	152(17)	226(21)	773(17)	
NSES (mean ± SD)	72.95±9.5	73.51±9.5	73.54±9.36	73.85±9.09	73.46±9.37	0.201
Social Support* (mean ± SD)	34.79±8.14	36.97±7.18	38.72±6.82	39.78±6.45	37.34±7.5	<i>p</i> <.001
<b>Sleeping hours, n (%)</b>						<i>p</i> <.001
<= 7 hours	353(27)	400(31)	313(35)	378(35)	1444(32)	
8~9 hours	512(39)	578(45)	382(43)	507(47)	1979(43)	
>= 10 hours	454(34)	312(24)	188(21)	186(17)	1140(25)	
Diabetes, n (%)	344(26)	248(19.22)	133(15)	138(13)	866(19)	<i>p</i> <.001
BMI, mean ± SD	29.03±6.18	28.33±5.81	27.21±5.04	26.81±4.88	27.95±5.64	<i>p</i> <.001
Depression, n (%)	189(14)	43(3.3)	16(1.8)	11(1)	259(5.7)	<i>p</i> <.001
Number of Chronic Diseases, mean ± SD	1.15±0.89	0.99±0.81	0.84±0.78	0.72±0.73	0.95±0.83	<i>p</i> <.001
<b>Self-Rated Health, n (%)</b>						<i>p</i> <.001
Excellent/very good	330(25)	598(46)	595(67)	853(80)	2371(52)	
Good	675(51)	618(48)	266(30)	213(20)	1776(39)	
Fair/poor	314(24)	77(6)	22(2)	5(0.5)	416(9)	

<b>Variable</b>	<b>Quartile 1 (0, 50] (n=1319)</b>	<b>Quartile 2 (50, 65] (n=1290)</b>	<b>Quartile 3 (65,75] (n=883)</b>	<b>Quartile 4 (75, 100] (n=1071)</b>	<b>Total participants (n=4563)</b>	<i>p</i> for Comparison
LLPA, min/d (mean ± SD)	180.4±50.62	187.9±48.17	192.68±48.81	197.42±47.95	188.84±49.39	<i>p</i> <.001
HLLPA, min/d (mean ± SD)	88.66±34.76	97.66±34.29	105.42±35.63	108.51±32.88	99.17±35.19	<i>p</i> <.001
MVPA, min/d (mean ± SD)	40.38±30.34	48.13±32.28	57.92±34.56	65.06±37.07	51.83±34.68	<i>p</i> <.001
Energy, kcal/day (mean ± SD)	1645.6±669.63	1630.23±645.91	1611.39±643.45	1528.45±612.3	1607.53±646.7	<i>p</i> <.001
aMED (mean ± SD)	3.99±1.85	4.18±1.83	4.43±1.83	4.46±1.91	4.24±1.87	<i>p</i> <.001
Fruits, cup equivalents (mean ± SD)	1.48±1.15	1.5±1.22	1.6±1.19	1.59±1.2	1.53±1.18	0.075
Vegetables, cup equivalents mean ± SD	1.37±0.85	1.44±0.9	1.6±0.99	1.62±1.05	1.49±0.95	<i>p</i> <.001
Nuts, ounce equivalents of lean meat mean ± SD	0.87±1.02	0.89±0.97	0.99±1.16	1.03±1.17	0.94±1.07	<i>p</i> <.01
Legumes, ounce equivalents of lean meat mean ± SD	0.36±0.52	0.4±0.6	0.4±0.58	0.45±0.69	0.4±0.6	<i>p</i> <.05
Whole grains, ounce equivalents mean ± SD	1.52±1.3	1.59±1.38	1.53±1.27	1.51±1.31	1.54±1.32	0.273
Fish, ounce cooked lean meat (mean ± SD)	0.67±0.7	0.74±0.79	0.8±0.79	0.78±0.84	0.74±0.78	<i>p</i> <.01
Ratio of monounsaturated to saturated fat	1.18±0.25	1.19±0.25	1.19±0.25	1.23±0.3	1.2±0.26	<i>p</i> <.001

<b>Variable</b>	<b>Quartile 1 (0, 50] (n=1319)</b>	<b>Quartile 2 (50, 65] (n=1290)</b>	<b>Quartile 3 (65,75] (n=883)</b>	<b>Quartile 4 (75, 100] (n=1071)</b>	<b>Total participants (n=4563)</b>	<i>p</i> for Comparison
Red and processed meat, ounce cooked lean meat (mean ± SD)	1.77±1.54	1.67±1.38	1.55±1.3	1.36±1.28	1.61±1.4	<i>p</i> <.001
Alcohol, gram/day (mean ± SD)	4.43±11.88	5.22±10.91	5.68±10.52	6.44±13.12	5.39±11.71	<i>p</i> <.01
Carbohydrate, gram/day (mean ± SD)	207.2±88.19	205.22±86.42	204.55±85.69	194.12±85.18	203.06±86.63	<i>p</i> <.001
Fat, gram/day (mean ± SD)	58.2±28.2	56.66±26.93	55.13±27.84	51.12±24.43	55.53±27.03	<i>p</i> <.001
Protein, gram/day (mean ± SD)	65.6±28.98	65.46±27.97	64.83±27.86	61.46±26.49	64.44±27.95	<i>p</i> <.001
Vegetable protein, gram/day (mean ± SD)	22.59±10.39	22.98±10.51	23.08±10.6	22.65±11.51	22.81±10.73	0.598
Animal protein, gram/day (mean ± SD)	42.82±22.33	42.57±21.33	41.74±21.69	38.86±20.65	41.63±21.61	<i>p</i> <.001

*Note.* aMED: Alternate Mediterranean diet. NSES: Neighborhood Social Economic Status. BMI: Body Mass Index; LLPA: low light physical activity; HLPa: high light physical activity; MVPA: moderate to vigorous physical activity.

\*Social support total score ranged from 9 to 45. Depression: items were a shortened version of the Center for Epidemiological Studies Depression Scale (CES-D), a score greater or equal to 0.06 as depressive. The number of self-reported chronic diseases was measured as the sum of chronic obstructive pulmonary disease, cardiovascular disease, cerebrovascular disease, cancer, osteoarthritis, and cognitive impairment.

**Table 4.2** Linear regression analysis for the associations of aMED levels as independent variables with the overall fatigue, energy and weariness outcomes (n=4563)

		M1 $\beta$ (95%CI)	M2 $\beta$ (95%CI)	M3 $\beta$ (95%CI)
<b>Overall Fatigue</b>	Quintile 1	Reference	Reference	Reference
	Quintile 2	0.32 (-2.07, 2.71)	0.43(-1.58, 2.44)	0.39(-1.6, 2.39)
	Quintile 3	2.81 (0.36, 5.24)*	2.15(0.09, 4.22)*	1.99(-0.06, 4.04)
	Quintile 4	2.91 (0.40, 5.42)*	2.19(0, 4.37)	1.92(-0.24, 4.09)
	Quintile 5	5.32 (2.94, 7.70)*	3.35(1.22, 5.48)*	2.99(0.88, 5.11)*
<b>Energy</b>	Quintile 1	Reference	Reference	Reference
	Quintile 2	1.09(-1.79, 3.97)	1.16(-1.24, 3.56)	1.13(-1.24, 3.50)
	Quintile 3	4.40(1.36, 7.45)*	3.43(0.87, 5.99)*	3.18(0.65, 5.71)*
	Quintile 4	4.60(1.53, 7.66)*	3.40(0.78, 6.03)*	2.98(0.38, 5.59)*
	Quintile 5	7.34(4.46, 10.22)*	4.61(2.08, 7.14)*	4.01(1.51, 6.53)*
<b>Weariness</b>	Quintile 1	Reference	Reference	Reference
	Quintile 2	-0.17(-2.5, 2.16)	-0.01(-2.11, 2.10)	-0.06(-2.16, 2.05)
	Quintile 3	1.63(-0.81, 4.08)	1.39(-0.87, 3.65)	1.30(-0.95, 3.56)
	Quintile 4	1.48(-0.98, 3.94)	1.36(-0.93, 3.65)	1.26 (-1.02, 3.54)
	Quintile 5	3.76(1.44, 6.08)*	2.59(0.35, 4.82)*	2.47 (0.24, 4.70)*

Note. Quintile 1. aMED ranged between [0, 2).

Quintile 2. aMED ranged between [2, 4).

Quintile 3. aMED ranged between [4, 5).

Quintile 4. aMED ranged between [5, 6).

Quintile 5. aMED ranged between [6, 9].

M1: unadjusted model

M2: adjusted for age, race/ethnicity, education, Neighborhood Socioeconomic Status (NSES), self-rated health, depression, BMI, number of chronic diseases, sleeping hours, social support, total energy, diabetes

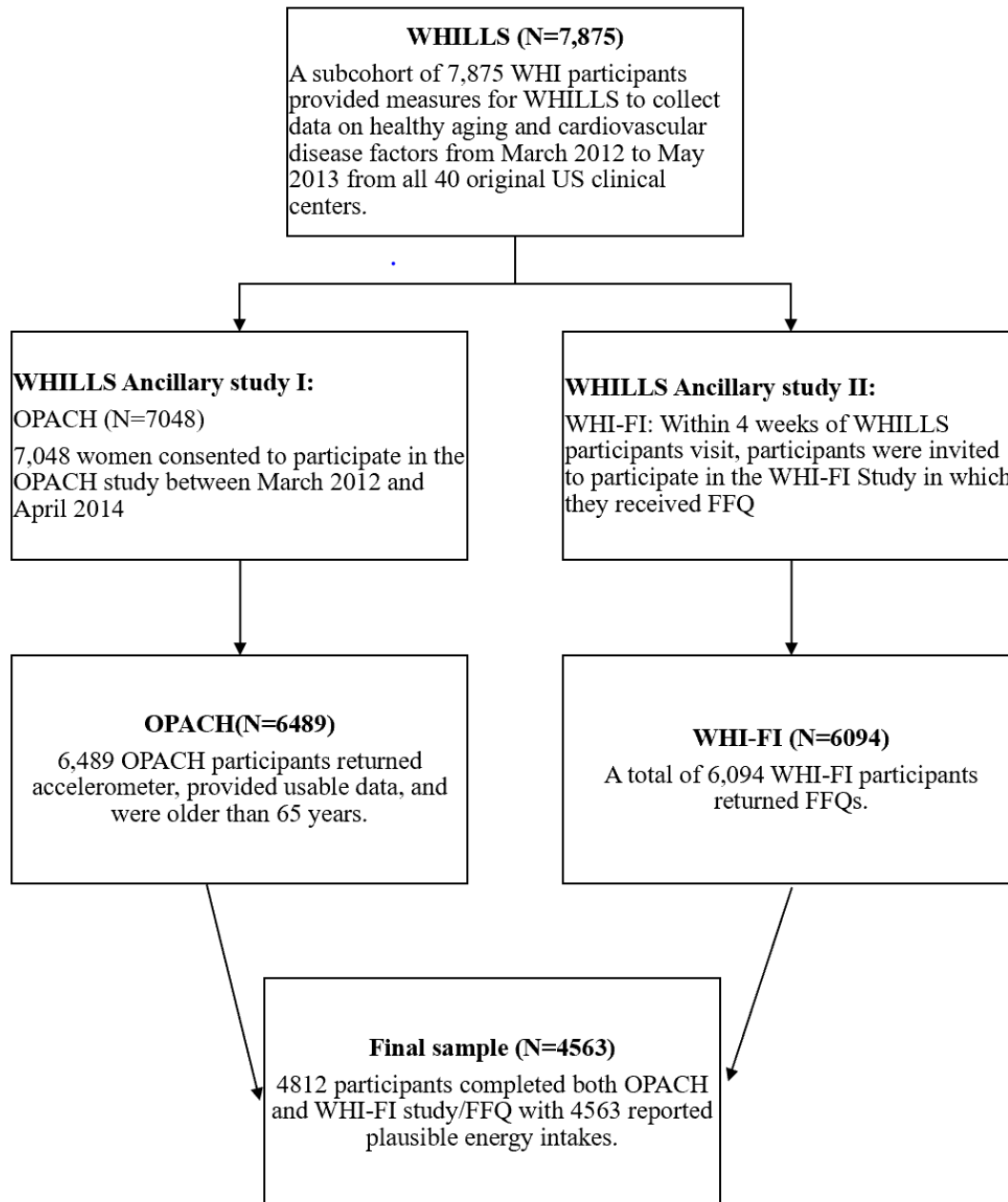
M3: adjusted for age, race/ethnicity, education, NSES, self-rated health, depression, BMI, number of chronic diseases, sleeping hours, social support, total energy, diabetes, low light physical activity time, high light physical activity time, moderate to vigorous physical activity time.

\* Significant at  $p < 0.05$

The number of chronic diseases: the sum of chronic obstructive pulmonary disease, cardiovascular disease, cerebrovascular disease, cancer, osteoarthritis, and cognitive impairment

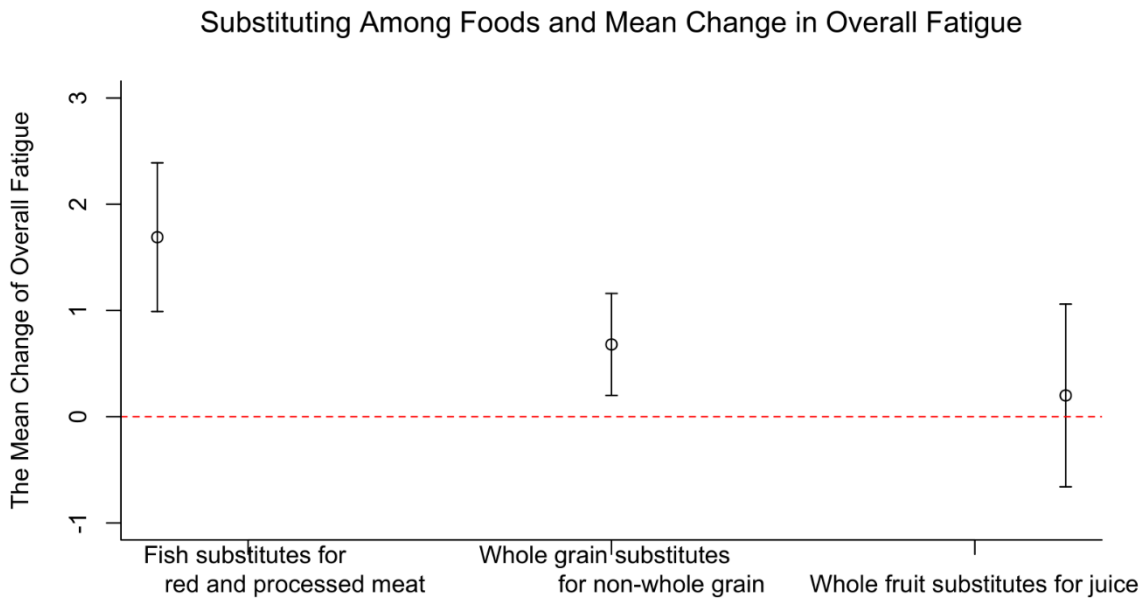
NSES: Neighborhood Social Economic Status

**Figure 4.1** Final analytical sample.



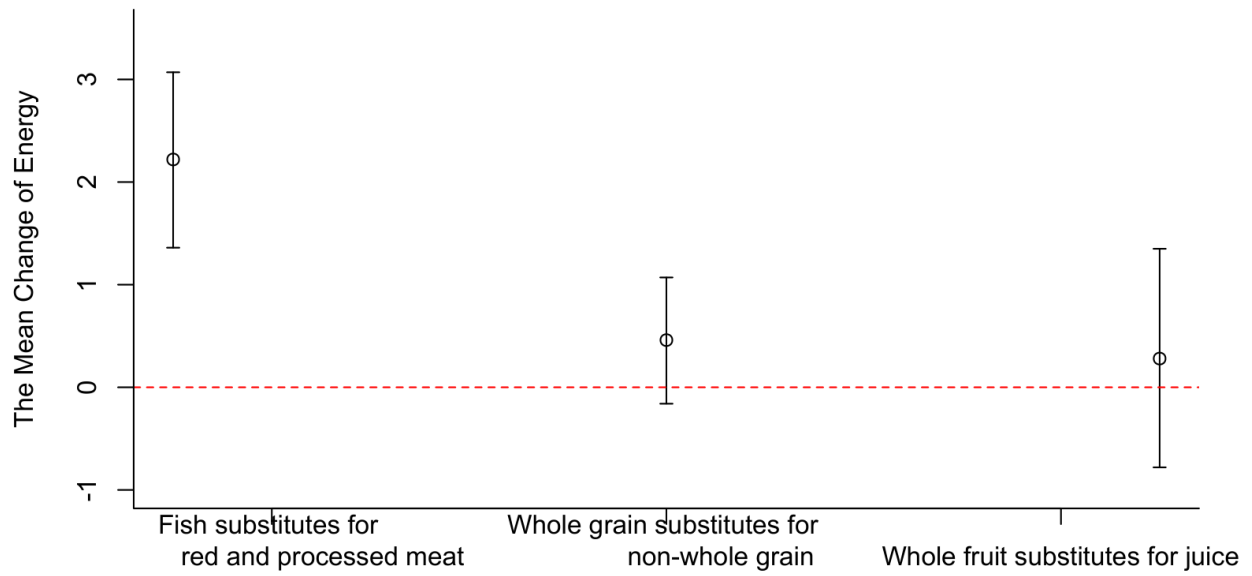
Among 7875 Women’s Health Initiative Long Life Study (WHILLS) participants, 7048 women consented to participate in the Objective Physical Activity and Cardiovascular Disease Health (OPACH) study, and 6489 OPACH participants returned their accelerometer with usable data and were older than 65 years. Meanwhile, a total of 6094 WHI-Food Intake (WHI-FI) study Food Frequency Questionnaires (FFQs) were returned by WHI LLS participants. Finally, 4812 participants completed both OPACH and FFQs measures with 4563 reporting plausible energy intakes. Thus, the final analytical sample size is 4563.

**Figure 4.2** Regression estimates from Isocaloric Substitution Models



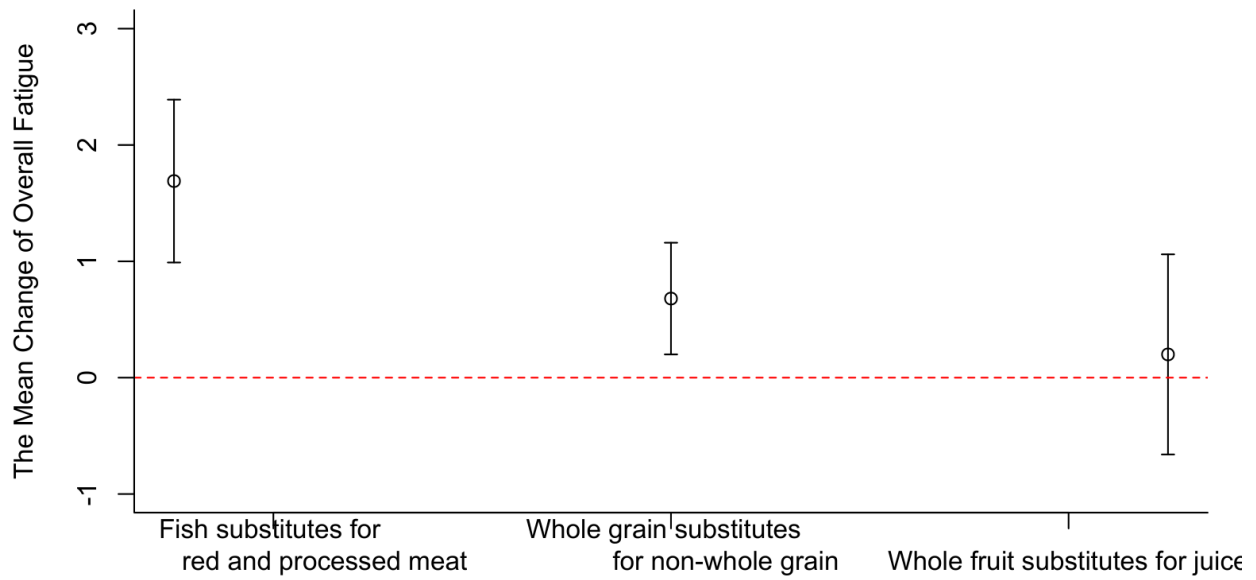
Regression estimates from Isocaloric Substitution Models of the mean score change in overall fatigue from substituting one-ounce cooked lean meat from fish for red and processed meat, substituting one-ounce equivalents whole-grain for non-whole grain, substituting one cup equivalent whole fruit for fruit juice.

### Substituting Among Foods and Mean Change in Energy



Regression estimates from Isocaloric Substitution Models of the mean score change in energy from substituting one-ounce cooked lean meat from fish for red and processed meat, substituting one-ounce equivalents whole-grain for non-whole grain, substituting one cup equivalent whole fruit for fruit juice.

### Substituting Among Foods and Mean Change in Overall Fatigue



Regression estimates from Isocaloric Substitution Models of the mean score change in weariness from substituting one-ounce cooked lean meat from fish for red and processed meat, substituting one-ounce equivalents whole-grain for non-whole grain, substituting one cup equivalent whole fruit for fruit juice.

**Supplementary Figure 4.1** The Adjusted Mean Values from Multiple Linear Regressions including interaction terms of the Associations of aMED with Overall Fatigue, Energy and Weariness Outcomes

