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DIET QUALITY, MORTALITY, AND PARKINSON DISEASE IN OLDER ADULTS: RESULTS FROM THE GEISINGER RURAL AGING STUDY

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Yi-Hsuan Liu

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The dissertation of Yi-Hsuan Liu was reviewed and approved by the following:

Xiang Gao
Associate Professor of Nutritional Sciences
Dissertation Advisor
Co-Chair of Committee

Gordon L. Jensen
Professor of Medicine and Nutrition
University of Vermont College of Medicine
Special Member

Penny M. Kris-Etherton
Distinguished Professor of Nutritional Sciences
Co-Chair of Committee

Muzi Na
Assistant Professor of Nutritional Sciences

Martin J. Sliwinski
Professor of Human Development and Family Studies

A. Catharine Ross
Professor of Nutrition and Physiology
Head of the Department of Nutritional Sciences

ABSTRACT

The proportion of our population that is older is growing at a substantial rate which may in turn be associated with increased public health burden. Identifying potentially modifiable lifestyle factors has thus been a high priority as the prevalence of age-related chronic disorders is expected to increase. Diet and nutritional status have been linked to risk of chronic disease and quality of life. In particular, older adults who are more likely to suffer from poor diet quality due to age-related metabolic changes may have higher risk of having chronic disease. Therefore, effectively detecting sub-optimal diet quality among older population, especially the oldest old who are 80 years and older, may help improve nutritional status and health outcomes. Development of an easy to administer and valid dietary screening tool suitable to examine diet quality in the oldest old would be a major step forward to better understand the relationship between diet quality and health outcomes in this population.

The objective of the first study was to conduct a validation analysis of a previously developed dietary screening tool (DST) to examine whether the DST would be a valid measure of diet quality among the oldest old. The DST was initially developed for older adults aged 65 years and older residing in rural Pennsylvania. In this study, we compared the DST scores with the Healthy Eating Index (HEI)-2015 scores, generated from three 24-hour dietary recalls, among 122 participants aged from 82 to 97 years in the Geisinger Rural Aging Study (GRAS). Pearson correlations were used to represent

concurrent validity after adjusting for potential confounders. Bland-Altman plot was utilized to examine whether there was consistent bias. After adjusting for potential confounders, we observed a significant correlation between the DST score and the HEI score in an age- and sex-adjusted model (adjusted r=0.68; p<0.001). Moreover, participants within the not-at-risk DST category had significantly higher HEI scores (adjusted means=79.6 ± 3.68) compared with those categorized as at-risk (adjusted means=51.2 ± 1.56) and possibly-at-risk (adjusted means=66.3 ± 1.79) (p-trend<0.001). We concluded that the DST is a valid dietary screening tool that may be used to assess overall diet quality among persons of advanced age. However, due to some study limitations, such as lack of energy estimate, high non-completion rate, and limited diversity in population, studies in other populations of older persons are needed.

The objective of the second study was to examine the association between overall diet quality, assessed by a validated DST, and risk of mortality in the oldest old. We hypothesized that participants with better diet quality would have lower risk of mortality. There were 1,990 participants (812 men and 1,178 women; mean age: 84.1 years old; age range: 80 to 102 at baseline) from the GRAS longitudinal cohort included in this study. We collected participants' baseline descriptive information using mailed surveys in 2009. Diet quality was also assessed in 2009 using the mailed DST, which consists of 25 food- and behavior-specific questions related to dietary consumption. The DST scores were determined based upon responses to individual questions and could range from 0 (lowest) to 100 (highest) with 5 potential bonus points for dietary supplement usage. Death was identified using both electronic medical record (EMR) and the social security death index

data. Hazard ratios (HRs) and 95% confidence intervals (CIs) across three diet quality categories were calculated using Cox proportional hazards models after adjusting for potential confounders, including age, sex, baseline body mass index (BMI), self- or proxy-reporting, smoking status, living arrangement, oral health status, and Charlson index of comorbidity score. During 8 years of follow-up (October 2009 to February 2018), there were 931 death cases identified. Having high diet quality (defined as DST scores >75) was associated with significantly lower mortality risk compared with having low diet quality (defined as DST scores <60) after adjusting for potential risk factors (adjusted HR=0.76; 95% CI: 0.59-0.97; *p*-trend=0.04). The observed association between diet quality and risk of mortality was not modified by potential risk factors for mortality, such as obesity and disease burden. Taken together, results from our prospective cohort suggest that diet quality, as assessed by the DST, is significantly associated with risk of mortality in the oldest old. Our findings may strengthen recognition of the roles of nutrition and overall diet quality in healthy aging. Some study limitations include reverse causality, under-reported smoking rate, and lack of repeated diet quality assessments. More prospective cohort studies are thus warranted to examine the generalizability of our findings and to provide evidence-based dietary recommendations for older population.

The objective of the third study was to investigate the association between diet quality and risk of Parkinson disease in adults aged 65 years and older using a prospective cohort design and a meta-analysis. We hypothesized that individuals with better diet quality would have lower risk of Parkinson disease. Our study included 3,653 participants who were free of Parkinson disease at baseline (1,519 men and 2,134

women; mean age of 81.5 years) in the GRAS cohort. Participants' diet quality was assessed using a validated DST including 25 food- and behavior-specific questions in 2009 (baseline). Electronic health records based on ICD9 (332.*), ICD10 (G20), and Parkinson-related treatments were used as the criteria to identify potential Parkinson cases. Incident Parkinson cases required two criteria, including being diagnosed at least 1 year after completing diet quality assessment and treatment with Parkinson-related medication(s). HRs and 95% CIs across diet quality tertiles were calculated using Cox proportional hazards models after adjusting for potential risk factors, including age, sex, race, educational level, smoking, oral health, obesity and living arrangement. After a mean follow-up period of 6.94 years, there were 47 incident Parkinson cases identified. Having high baseline diet quality was associated with lower risk of Parkinson disease compared with having low diet quality at baseline (adjusted HR for the highest vs the lowest diet quality tertiles=0.39; 95% CI: 0.17-0.89; *p*-trend=0.02). Moreover, we performed a meta-analysis by systematically searching in PubMed, Web of Science, and the Cumulative Index for Nursing and Allied Health databases from January 1, 1981 to November 6, 2019. We further combined our study results with four previously published studies that we identified that were related to this topic. Observational studies, including prospective, retrospective, and case-control studies, which examined the association between overall diet quality or dietary pattern in relation to Parkinson disease met our inclusion criteria. Pooled risk ratios and 95% CIs were calculated using random-effects model. Our meta-analysis of 6 study populations including 140,617 individuals also showed that adherence to a high-quality diet was associated with lower risk of Parkinson disease (pooled risk ratio=0.64; 95% CI: 0.49-0.83). Based upon our findings in the

prospective cohort and the meta-analysis, having high diet quality was associated with lower risk of developing Parkinson disease. Notably, due to some study limitations, for example, reverse causality in our cohort analysis and various methods of dietary assessment utilized across the included studies in our meta-analysis, our findings should be interpreted with caution.

In conclusion, findings from the first of our three studies suggest that the DST is a valid measure of diet quality among older adults that may be used to measure diet quality in the oldest old (≥80 years). In our 2nd study we found that high diet quality, as assessed by the DST, was associated with lower risk of mortality among the oldest old. In our 3rd study we found an association between high diet quality and lower risk of Parkinson disease in older adults aged 65 years and older. Similarly, our meta-analysis of observational studies showed that high diet quality was associated with lower risk of Parkinson disease. Additional longitudinal studies with other aging populations with longer follow-up and larger sample size are warranted to test the generalizability of our DST findings from the GRAS cohort in order to better provide dietary recommendations for healthy aging.

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LIST OF ABBREVIATIONS

95% CI	95% confidence interval
AARP	American Association of Retired Persons
AHEI	alternate Healthy Eating Index
BMI	body mass index
CINAHL	Cumulative Index for Nursing and Allied Health
DASH	Dietary Approaches to Stop Hypertension
DST	dietary screening tool
EHR	electronic health record
EMR	electronic medical record
GRAS	Geisinger rural aging study
HDL	high density lipoprotein
HEI	Healthy Eating Index
HR	hazard ratio
ICD	International Classification of Diseases
kg	kilograms
LDL	low density lipoprotein
MCMC	Markov chain Monte Carlo
mg/dL	milligrams per deciliter
NCC	Nutrition Coordinating Center
NDSR	Nutrition Data System for Research
NIH	National Institutes of Health
OR	odds ratio
RR	relative risk
SAS	Statistical Analysis Software

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CHAPTER 1

INTRODUCTION

Background

Populations are aging across the globe with an accompanying public health burden. The proportion of the population that is older is growing at a significant rate along with the prevalence of chronic disease. Based on U.S. Census Bureau data, 20% of the population is projected to be older adults (aged 65 years and older) while more than 60% will be managing more than one chronic condition by 2030 (1). As life expectancy continues to grow worldwide, the prevalence of age-related functional decline and chronic conditions are expected to increase rapidly (2). Therefore, to promote healthy aging it is critical to identify potentially modifiable lifestyle factors that may prevent or reduce the onset of chronic disease and related mortality.

Diet has been suggested as one of the important lifestyle factors in healthy aging (3-5). In particular, diet quality or dietary pattern representing general eating pattern has been associated with several chronic conditions, including overweight/obesity (6-9), diabetes (10, 11), cardiovascular disease (12, 13), metabolic syndrome (14), some types of cancer (15-17), and mortality (18-20). However, limited studies have prospectively examined the association between overall diet quality and risk of comorbidities and related mortality in older adults aged ≥65 years (21), especially the oldest old aged ≥80 years. Research has been limited due to lack of an effective dietary screening tool that can be readily applied to assess older adults' diet quality. The relationships between diet quality, assessed by a validated screening tool, and comorbidities as well as mortality in older adults aged ≥65 years and the oldest old aged (≥80 years) warrant further investigation.

Objectives

The goals of my dissertation research included testing whether a previously developed Dietary Screening Tool (DST) is a valid measure of diet quality among the oldest old and to further examine whether overall diet quality, as assessed by the DST, is associated with altered risk of mortality and Parkinson disease. Through these studies, we can help identify potentially modifiable dietary and lifestyle factors to promote healthy aging and improve quality of life for aging individuals. We can also help address key knowledge gaps and provide evidence-based recommendations for our older population.

Three primary objectives were therefore investigated for partial fulfillment of this dissertation research project:

Objective 1: To perform validation analyses to test application of the DST among the oldest old

Objective 2: To prospectively examine the association between diet quality as assessed by the DST and risk of mortality in the oldest old

Objective 3: To examine the association between diet quality as assessed by the DST and risk of Parkinson disease in a prospective cohort including older adults and in a meta-analysis

The Geisinger Rural Aging Study (GRAS) is the longitudinal cohort that was used to investigate these objectives (Figure 1.1). The GRAS cohort was initiated in 1994 in central Pennsylvania and included 21,645 community-dwelling older adults ≥65 years

enrolled in a Medicare-managed health organization through the Geisinger Health System. The GRAS cohort has limited diversity with mainly white and non-Hispanic participants. Detailed information regarding the GRAS cohort has been described previously (22).

Objective 1 was based on a cross-sectional subset of the GRAS cohort of community-dwelling participants aged ≥80 years during 2015 to 2016. The recruitment of participants in objective 1 was completed in five steps: 1) completed screening of surviving GRAS participants 80 years or older (n=1,556); 2) contacted participants without dementia based on ICD9 290.** diagnosis and who met inclusion criteria using electronic medical record (EMR) review (n=1,201); 3) completed final screening questions and questionnaires among participants consenting to be enrolled in this study (n=174); 4) administered a phone interview to collect diet quality, anthropometric data, and functional status; and 5) conducted three dietary recalls via telephone. After excluding participants with missing both DST score and three-day dietary recalls (n=47), missing DST score only (n=3), and missing three-day dietary recalls only (n=2), 122 participants remained for final analysis in objective 1.

Objectives 2 and 3 were based on the main GRAS cohort using data available in October 2009 as baseline. For objective 2, survey questionnaires containing health status, demographic and descriptive information, and the DST were sent via mail to 3,901 surviving GRAS participants who were ≥80 years in 2009. Of the participants that were sent mailed surveys, 2,721 participants returned completed questionnaires. Participants with unknown comorbidity disease status (data could not be obtained through medical

claims and/or through the electronic medical records (EMRs) or lost to follow up) were excluded, resulting in 1,990 remaining participants who were followed through February 2018 and included in the primary data analysis.

For objective 3, mailed survey questionnaires were sent to 5,939 surviving GRAS participants in 2009 to collect health status, demographic and descriptive information, and the DST. Of the participants that were sent mailed surveys, 4,020 participants returned completed questionnaires. After excluding participants with Parkinson disease at baseline and individuals who were lost to follow up, a total of 3,653 participants remained that were included in the primary data analysis.

Approval for implied consent through completion of the mailed surveys was obtained from the Office of Research Protections at The Pennsylvania State University and the Human Research Protection Program of the Geisinger Health Systems Institutional Review Board.

Dissertation content and format

This dissertation starts with a review of literatures in Chapter 2. In Chapter 3, 4, and 5, the detailed results and findings of objective 1, 2, and 3 are reported and discussed, respectively. Chapter 6 concludes this dissertation with conclusions, strengths and limitations, and future directions. The contents presented in Chapter 3 and 4 has been published in the *Journal of Nutrition in Gerontology and Geriatrics* and the *Journal of the American Geriatrics Society*, respectively. Tables, figures, supplementary materials, and appendices are placed at the end of each chapter.

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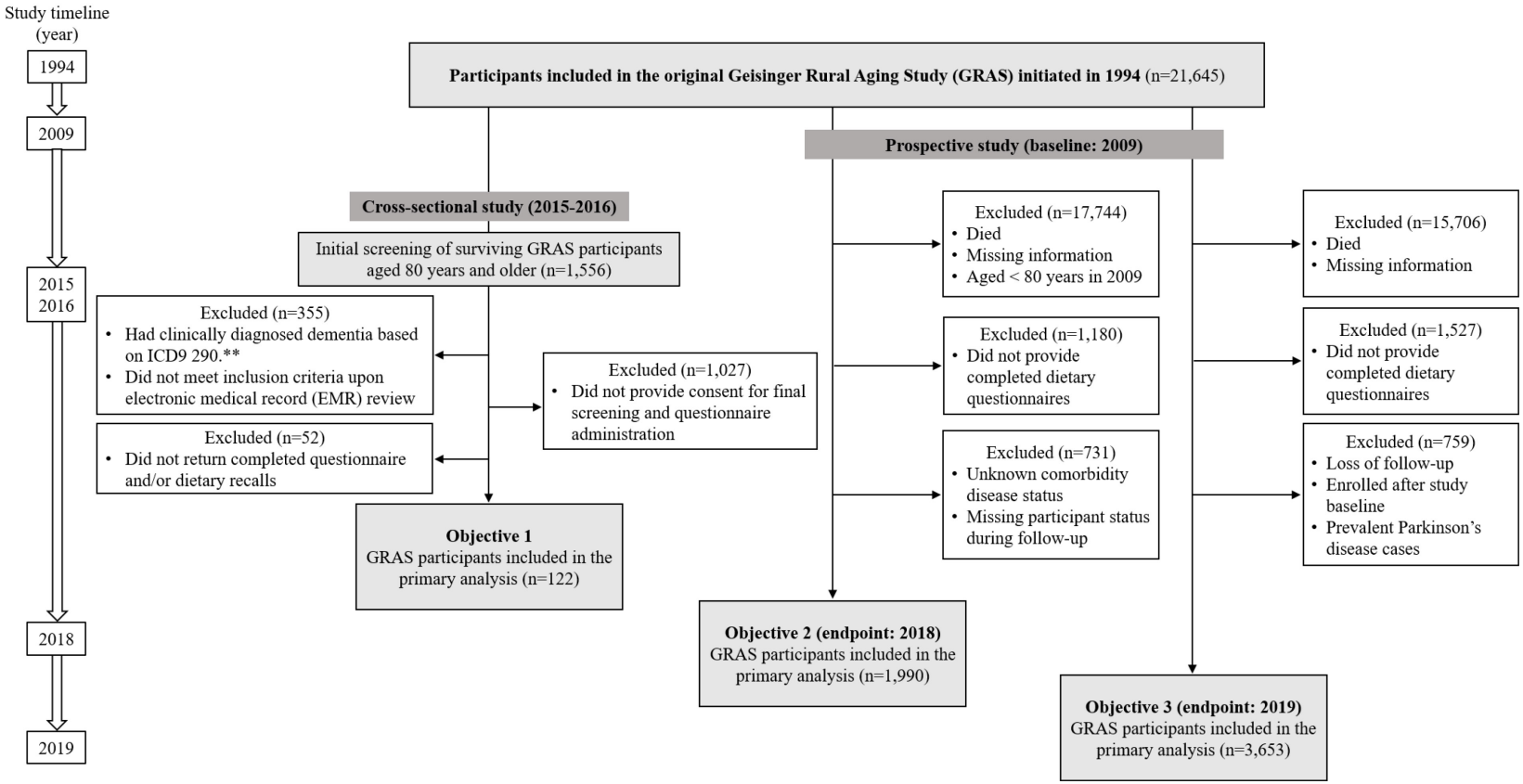

Figure 1.1. Flow chart of the Geisinger Rural Aging Study (GRAS) participants

CHAPTER 2

LITERATURE REVIEW

This chapter includes a review of the literature focusing on 1) methods of dietary evaluation; 2) the association between overall diet quality and risk of mortality; and 3) the association between overall diet quality, dietary pattern, and risk of neurodegenerative diseases, especially Parkinson disease.

Introduction

Older adults are a rapidly growing segment of the world's population and will soon represent 1 in 5 Americans (1). Persons aged 85 years and over are predicted to grow from 6 million in 2014 to 20 million by 2060 (1). With expanding medical resources, increased availability of potable water, and improved environmental hygiene, life expectancy is expected to continue to advance, which may further enhance expansion of the older adult population (2). As people live longer and older population enlarges, the prevalence of age-related chronic conditions and functional decline are also likely to increase. It is therefore a public health priority to promote healthy aging though modifiable lifestyle factors to improve the years of sound quality of life that is free of major chronic conditions and frailty.

Diet is a modifiable lifestyle factor that may be associated with health outcomes at all ages (3). In particular, recent studies have shifted toward focusing on the impact of overall diet quality or dietary pattern because dietary components included in the diet are usually ingested in combination instead of consuming single foods or nutrients (4-6). Examining overall diet quality or dietary pattern may provide better understanding of the role of diet in disease development as some methodological limitations, such as nutrient-nutrient interactions and collinearity, can be addressed (4-6).

A number of observational studies have examined the association between overall diet quality and risk of chronic disease and mortality. For example, the Mediterranean diet, representing the traditional dietary patterns in the countries near the Mediterranean

sea, is characterized by increased consumption of plant-based foods and reduced intake of red meat and saturated fats (7). Several observational studies show that adherence to the Mediterranean diet is associated with lower risk of all-cause mortality (8-12), cardiovascular disease (8, 11-13), cancer (11, 12), diabetes (12), cognitive decline (14-17), and dementia and Alzheimer's disease (11, 14-17). However, limited longitudinal cohort studies have examined the associations between diet quality, dietary pattern, and risk of mortality and comorbidities in older populations that are more susceptible to poor diet quality and adverse health conditions due to age-related metabolic changes (18). Our ability to better understand the relationship between diet quality and risk of chronic disease has historically been limited by the absence of valid dietary screening assessments developed for older adults aged ≥65 years, especially the oldest old aged ≥80 years.

Methods of dietary evaluation: the need for a dietary screening tool

As dietary components are usually not consumed in isolation, epidemiological studies have recently shifted the focus from single nutrient or dietary component to comprehensive diet quality or dietary pattern analysis (5, 19, 20). Assessing overall diet quality or dietary pattern can reflect the usual consumption of food components and address limitations existing in studies that focus on a single dietary component or a combination of selective nutrients. Importantly, nutrient-nutrient interactions and collinearity, which have been the major concerns in single dietary component analyses, can be addressed in dietary pattern analyses (4). With increasing numbers of clinical trials failing to show protective effects of single nutrients on risk of chronic disease, dietary pattern analysis offers promising potential to better address the role of diet on health-related consequences (20).

Dietary assessment can be conducted primarily using two methods, *a priori* assessment and *a posteriori* assessment. Diet quality evaluated by *a priori*, also known as hypothesis-driven approaches, are based on adherence to established dietary guidelines, known healthy dietary patterns, or cultural dietary patterns. Examples include the Healthy Eating Index (HEI), the Dietary Approaches to Stop Hypertension (DASH) diet, and the Mediterranean diet. Evaluation of dietary pattern using *a posteriori*, also known as data-driven approaches, depends on generating food pattern groups from collected dietary responses utilizing statistical techniques. Examples of *a posteriori* assessment include principal component analysis, cluster analysis, and reduced rank regression.

Both *a priori* and *a posteriori* dietary assessments have been used to study the relationships between overall diet quality and health outcomes. However, with *a priori* approaches, wide variations of included food components and scoring scales among different diet quality indices could lead to heterogeneity and in turn impact study generalizability (5, 20, 21). To be more specific, diet quality indices initially developed in the European countries and the United States, such as the Mediterranean diet, the HEI, and the DASH diet, may not be applicable for cohorts with different demographic characteristics without being modified based on culture-related dietary habits. In contrast, dietary patterns generated using *a posteriori* methods that are specific for cohort participants may better reflect overall dietary habits and culture in the region to be evaluated. However, the reliability of *a posteriori* approaches relies heavily on statistical methodology and the findings may be limited to use in certain populations (5, 20-23).

In addition to limitations in approaches to diet quality evaluation, assessing dietary intake by commonly-used subjective assessment methods, including food-frequency questionnaire, food records, or 24-hour dietary recalls, is particularly challenging for older persons (24). These methods have some types of errors. For example, respondent and recorder errors, interviewer and reviewer errors, database errors are commonly observed in 24-hour dietary recalls and food records, while measurement errors may occur in food frequency questionnaire (25). These dietary intake assessments are not practical to be routinely used in clinical settings due to cost effectiveness and resources required. Difficulties in collecting accurate dietary intake for diet quality assessment may result.

Because of the disadvantages in existing diet quality evaluations and dietary intake assessments, a dietary screening tool is needed that is easily-administered and can readily identify overall diet quality among older adults. Using a dietary screening tool developed for older adults who are more vulnerable to poor diet quality, initial screening results can help determine whether additional follow-ups and dietary interventions are needed in order to prevent the onset of negative health outcomes.

The GRAS research team previously developed the Dietary Screening Tool (DST), consisting of 25 food- and behavior-specific questions, that has been validated among older adults aged 65 years and over living in rural Pennsylvania (26, 27). The DST development includes three phases: 1) using cluster analysis to characterize dietary patterns based on dietary intake data collected from 179 older adults and to further develop questionnaire; 2) conducting cognitive interviewing of questionnaire among 17 older adults to assist in refining components included in the questionnaire; and 3) finalizing the DST scoring algorithm that classified participants based on diet quality and further relating diet quality categories to nutritional biomarkers among 206 older adults (26). Validation analyses of the DST among 204 older adults aged ≥65 years demonstrated that diet quality categories classified by the DST were associated with food and nutrient intake estimated from 24-hour dietary recalls and biochemical indicators of nutritional status (27). Further validation analyses of the DST against other diet quality indices and nutritional biomarkers in cohorts with different ethnic groups, individuals aged ≥80 years, and more diverse lifestyle factors are required to ensure the effectiveness and generalizability of this instrument.

Diet quality and risk of mortality in older adults

The leading cause of death has shifted over time from infectious disease to chronic disease in developed countries (28, 29). Because of this transition, the identification of modifiable risk factors of chronic disease is a high priority (30). Accumulated evidence from observational studies has emerged to support the role of healthy dietary patterns on lower risk of all-cause mortality (31-33). In a recent systematic review and meta-analysis of 29 prospective studies including 1,676,901 participants, it was observed that a 2-point increment in adherence to the Mediterranean diet was associated with lower risk of all-cause mortality (pooled hazard ratio (HR)=0.90; 95% confidence interval (CI): 0.89-0.91) and there was a significant linear inverse association between the Mediterranean diet adherence and all-cause mortality risk (33). Another systematic review and meta-analysis of 13 prospective studies also found that high diet quality, as assessed by the HEI, the Alternate Healthy Eating Index (AHEI), and the DASH diet score, was associated with lower risk of all-cause mortality (pooled RR for the highest vs the lowest quality=0.78; 95% CI: 0.77-0.80) (32). However, most of the prospective studies that have examined the relationship between diet quality and all-cause mortality have not focused on older persons. Better understanding the impact of diet on overall survival among older persons would assist in developing evidence-based dietary guidelines to promote healthy aging.

Review of the literature revealed no systematic review or meta-analysis of observational studies investigating the association between overall diet quality and risk of all-cause mortality restricted to an older adult population. In a prior narrative review

including 16 prospective studies conducted among older adults aged 60 years and over, it was observed that studies using *a posteriori* dietary assessments showed consistent inverse associations between dietary pattern and risk of mortality, while studies using *a priori* dietary assessments generated mixed findings (34).

With regard to individual prospective studies, the relationship between diet quality and risk of all-cause mortality depends on the method of dietary assessment. In a prospective study conducted among 972 older adults aged 65 years and older in the British Diet and Nutrition Survey, having high diet quality, assessed by the Mediterranean diet score (adjusted HR=0.78; 95% CI: 0.62-0.98) and the Recommended Food Score (adjusted HR=0.67; 95% CI: 0.52-0.86), was associated with lower risk of all-cause mortality after a mean of 14 years of follow-up, however, no significant association was observed when assessing diet quality by the Healthy Diet Score (adjusted HR=0.99; 95% CI: 0.79-1.24) (35). Similarly, in a prospective study including 3,328 men with a mean age of 60 years in the British Regional Heart Study, having high diet quality, as assessed by the Elderly Dietary Index, was found to be associated with lower risk of all-cause mortality during a mean of 11.3 years of follow-up (adjusted HR=0.75; 95% CI: 0.60-0.94; *p*-trend=0.03) (36). However, no significant association was observed when assessing diet quality by the Healthy Diet Indicator (adjusted HR=0.96; 95% CI: 0.72-1.29; *p*-trend=0.46) (36).

Consistent findings across different diet quality indices were also observed in selected studies. A prospective study including 63,805 postmenopausal women with a mean age of 60 years from the Women's Health Initiative Observational Study showed

that better adherence to a high-quality diet, as assessed by the HEI (adjusted HR=0.76; 95% CI: 0.70-0.83), the AHEI (adjusted HR=0.82; 95% CI: 0.76-0.90), the alternate Mediterranean diet score (adjusted HR=0.74; 95% CI: 0.68-0.81), and the DASH score (adjusted HR=0.76; 95% CI: 0.70-0.83), was associated with lower risk of all-cause mortality after 12.9 years of follow-up (37). Another prospective study including 29,634 postmenopausal women with a mean age of 61.4 years at baseline in the Iowa Women's Health Study also found that high diet quality, as assessed by AHEI (adjusted HR=0.82; 95% CI: 0.77-0.87; *p*-trend<0.001) and A priori score (adjusted HR= 0.80; 95% CI: 0.76-0.85; *p*-trend<0.001), was associated with lower all-cause mortality risk after a mean of 20.3 years of follow-up (38). Likewise, a prospective study including 492,823 participants with a mean age of 60 years from the National Institutes of Health (NIH)-American Association of Retired Persons (AARP) Diet and Health Study showed that better adherence to the HEI-2010 (adjusted HR for men=0.78; 95% CI: 0.76-0.80; adjusted HR for women=0.77; 95% CI: 0.74-0.80), the AHEI-2010 (adjusted HR for men=0.76; 95% CI: 0.74-0.78; adjusted HR for women=0.76; 95% CI: 0.74-0.79), the alternate Mediterranean diet (adjusted HR for men=0.77; 95% CI: 0.75-0.79; adjusted HR for women=0.76; 95% CI: 0.73-0.79), and the DASH diet (adjusted HR for men=0.83; 95% CI: 0.80-0.85; adjusted HR for women=0.78; 95% CI: 0.75-0.81) was associated with lower risk of all-cause mortality after 15 years of follow-up (39).

Although evidence from existing prospective studies tends to suggest a link between a high-quality diet and lower risk all-cause mortality among older adults aged ≥60 years, it appears that different dietary assessment tools utilized in assessing diet

quality may affect the observed relationship with risk of all-cause mortality. One of the possible explanations may be various dietary components and scoring scales incorporated among different diet quality indices. Therefore, a dietary screening tool that is valid for application in an older adult population may provide more useful data in screening overall diet quality. The DST was developed in 2009 among the GRAS participants aged 65 years and older and was shown to be a valid measure of diet quality in older adults residing in rural Pennsylvania (26, 27). In a previous GRAS prospective study including 2,995 older adults aged 65 years and over, it was observed that having low diet quality, as assessed by the DST, was associated with higher risk of all-cause mortality after a mean of 3.1 years of follow-up (adjusted HR for the lowest vs the highest diet quality=1.53; 95% CI: 1.06-2.22) (40). However, prospective studies examining the association between diet quality and mortality among the oldest old aged ≥80 years are limited. More large-scale prospective studies conducted among this advanced age population are thus warranted to better address the relationship between overall diet quality, age-related functional decline, and risk of all-cause mortality.

Diet quality, dietary pattern, and neurodegenerative disease

The prevalence of age-related neurodegenerative disorders, including dementia, Alzheimer's disease, and Parkinson disease, is expected to increase as people are living longer (41, 42). In the United States, it is estimated that 1 in every 10 people aged 65 years and older has Alzheimer's dementia, which is the most common type of dementia, and the prevalence is predicted to increase (43, 44). Furthermore, in 2011 the prevalence of all types of dementia for older adults in the United States age 80 to 84, 85 to 89, and 90 and over was estimated to be 15.3%, 24%, and 36.2%, respectively (1). A similar rising trend of prevalence is observed in Parkinson disease that more than one million people in the United States may have Parkinson disease by 2030 (45). Of note, Parkinson disease accounts for approximately 3.6% of dementia cases (46). It is therefore critical to find out potential effective and efficient strategies to delay the onset and progression of neurodegeneration.

Some systematic reviews and meta-analyses of observational studies and randomized controlled trials have suggested better adherence to high diet quality or a healthy dietary pattern may be associated with improved cognitive function (15, 17, 47), lower risk of dementia (15), decreased risk of Alzheimer's disease (15), and reduced risk of overall neurodegenerative disease (11), all of which highlight the important role of overall diet quality in age-related cognitive decline. However, prospective studies examining diet quality and risk of overall dementia in older adults are relatively limited and mixed results have been observed. A French study including 1,410 older adults found that high adherence to the Mediterranean diet was not associated with dementia risk after

4.1 years of follow-up (adjusted HR=1.12, 95% CI: 0.60-2.10) (48). Another study conducted among 1,141 older adults in the Midwestern United States also observed no significant association between the Mediterranean diet adherence and risk of incident dementia during 2.2 years of follow-up (adjusted HR for high vs low adherence=0.79, 95% CI: 0.51-1.21; adjusted HR for high vs middle adherence=0.75, 95% CI: 0.46-1.21) (49). In contrast, it was observed that better adherence to the Mediterranean diet was associated with lower risk of incident Alzheimer's disease after 3.8 to 5.4 years of follow-up in cohorts that included approximately 2,000 older adults in New York City area (adjusted HR for high vs low adherence=0.60, 95% CI: 0.42-0.87 (50); adjusted HR for high vs low adherence=0.79, 95% CI: 0.66-0.94 (51); adjusted HR for high vs low adherence=0.56, 95% CI: 0.36-0.86 (52)). In a US cohort including 2,148 older adults, it was also found that better adherence to a healthy dietary pattern, characterized as high intake a omega-3 and omega-6 polyunsaturated fatty acids, vitamin E, and folate as well as low consumption in saturated fats and vitamin B12, was associated with lower risk of Alzheimer's disease after 3.8 years of follow-up (adjusted HR for high vs low adherence=0.62, 95% CI: 0.43-0.89) (53)

Although findings from observational studies tend to indicate an inverse association between diet quality and risk of dementia, a recent prospective study investigating the relationship between repeated diet quality evaluations at midlife and risk of dementia among 8,225 participants with a mean age of 50.2 years found no significant association after 24.8 years of follow-up (54), suggesting that different lengths of follow-up among different studies may have an impact on inconsistent findings.

Parkinson disease is the second most common neurodegenerative disease. The most important clinical feature is degeneration and loss of dopaminergic neurons in the substantia nigra (55, 56). During the development of Parkinson disease, misfolding and aggregation of α-synuclein, which is the primary protein component of Lewy bodies, can spread and contribute to the death of host neurons. These neurodegenerative changes culminate in clinically manifest in movement disorders (55-59). Due to the pathological processes of Parkinson disease, neuroinflammation and oxidative stress are likely to be involved in disease development (56, 59-63). In addition, recent studies suggest that α-synuclein aggregation may initially occur in the gut and then be transported to the brain through gut-brain axis. These observations further suggest that gut microbiota and bacterial metabolites may also play a role in regulating the pathogenesis and progression of Parkinson disease (57, 64-67). Taken together, a compelling case can be made for a potential link between diet quality, dietary pattern, and risk of Parkinson disease.

While systematic reviews or meta-analyses of observational studies that investigated the association between diet quality and risk of Parkinson disease have not been reported, some prospective and case-control studies are available. A prospective study including 131,368 participants from the Health Professional Follow-Up Study and the Nurses' Health Study in the United States with mean age ranging from 48.8 to 56.5 years at baseline showed that better adherence to the prudent dietary pattern, characterized as high intakes of fruits, vegetables, legumes, whole grains, poultry, and fish, was associated with lower risk of incident Parkinson disease after 16 years of follow-up (p-trend=0.04) (68). A similar association was observed using the Alternate

Health Eating Index (AHEI) to assess diet quality (adjusted RR for the highest vs the lowest adherence=0.70; 95% CI: 0.51-0.94; *p*-trend=0.01) (68). A case-control study including 455 older adults residing in the New York City area with a mean age around 70 years found that high adherence to the Mediterranean diet was associated with lower odds of having Parkinson disease (adjusted OR for high vs low adherence=0.48, 95% CI: 0.28-0.82) (69). Likewise, another case-control study including 617 Japanese participants with a mean age of 67.4 years also found that high adherence to a healthy dietary pattern, characterized by high contents of vegetables, seaweed, pulses, mushrooms, fruits, and fish, was associated with lower odds of having Parkinson disease (adjusted OR for high vs low adherence=0.54; 95% CI: 0.32-0.92) (70). In contrast, a study conducted in Finland including 4,524 participants with a mean age of 53.3 years at baseline observed no significant association between diet quality, assessed by the modified AHEI derived from dietary history interview, and risk of incident Parkinson disease after 41 years of follow-up (*p*-trend>0.05 for both males and females) (71).

Due to the limited number of studies that have examined the association between overall diet quality and risk of Parkinson disease, large-scale prospective studies, especially in older adults who have higher risk of suffering from age-related neurodegenerative disorders, are needed to address the existing knowledge gap regarding the role of diet on the development of Parkinson disease. In addition, systematic reviews and meta-analyses are also warranted to extract current evidence to further guide the development of prospective studies and promote better understanding of the interaction between diet quality and neurodegeneration.

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CHAPTER 3

VALIDATION OF A DIET QUALITY SCREENING TOOL FOR USE IN THE OLDEST OLD

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*Additional analyses conducted for this dissertation are placed in the end of this chapter as appendices.

Validation of a diet quality screening tool for use in the oldest old

Yi-Hsuan Liu, MS, RD[1], Xiang Gao, MD, PhD[1], Diane C. Mitchell, MS, RD[1], G. Craig Wood, MS[2], Regan K. Bailey, PhD, MPH, RD, CPH[3], Christopher D. Still, DO, FACP, FTOS[2], and Gordon L. Jensen, MD, PhD[4]

[1] Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA;

[2] Department of Internal Medicine and The Obesity Institute, Geisinger Health System, Danville, PA;

[3] Department of Nutrition Science, Purdue University, West Lafayette, IN;

[4] Larner College of Medicine, University of Vermont, Burlington, VT

Corresponding author

Xiang Gao, MD, PhD

Associate Professor

Department of Nutritional Sciences, The Pennsylvania State University

109 Chandlee Laboratory, University Park, PA 16802

Phone: 814-867-5959

Email: xxg14@psu.edu

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*A PDF copy of the Dietary Screening Tool (DST) is available upon request.

Abstract

The oldest old (aged ≥80 years) are often the population subgroup at high nutritional risk due to age-related metabolic changes. We performed a validation analysis of a dietary screening tool (DST) which was developed for older adults among the oldest old. We examined dietary intakes using three 24-hour dietary recalls and the DST among 122 participants (aged 82 to 97) of the Geisinger Rural Aging Study. DST scores were compared with the Health Eating Index (HEI)-2015 scores, which were calculated based on three-day dietary recalls. Pearson correlations were used to characterize concurrent validity and Bland-Altman plots were used to identify potential bias. DST scores were significantly correlated with HEI scores (adjusted r=0.68; p<0.001) in an age- and sex-adjusted model. Those within the not-at-risk DST group had significantly higher HEI scores (adjusted means=79.6 ± 3.68) compared with those who were in the at-risk (adjusted means=51.2 ± 1.56) and the possibly-at-risk (adjusted means=66.3 ± 1.79) groups (p-trend<0.001). The DST appears to be a valid measure of diet quality in the oldest old when compared with the HEI and may be a potential tool to assess overall diet quality in this population.

Key words: Diet assessment; Diet quality; Oldest old; Geriatric nutrition

Introduction

Older adults are often at high risk of having poor nutritional status due to age-related functional declines and metabolic changes that may in turn be associated with adverse health conditions (1-3). Sound nutritional status can help aid prevention and recovery from illness or medical procedures (4). Older adults are a burgeoning segment of the U.S. population, soon representing 1 in 5 Americans (5). Therefore, early detection of older adults with compromised diet quality, such as inadequate consumption of fruits, vegetables, proteins, and whole grains or high intake of saturated fats and added sugars, can help to support a public health priority to improve nutritional status. However, among the oldest old (≥80 years of age), the role of diet quality in relation to nutritional status and health outcomes is relatively unknown. One limitation to better understanding of these issues is that to our knowledge there is currently no diet quality screening tool available that has been validated for use in the oldest old.

We previously developed a dietary screening tool (DST) that is a validated measure of diet quality in adults aged ≥65 years residing in rural Pennsylvania and the DST was validated in middle-aged cohort in Appalachia recently (6-8). In this current study, we determined whether the previously developed DST would also be a valid measure of diet quality among a cohort of the oldest old. We hypothesized that the DST score would be significantly correlated with Healthy Eating Index (HEI)-2015 score, reflecting degree of adherence to the Dietary Guidelines for Americans, based on three-day dietary recalls among the oldest old.

Methods

Study population

The Geisinger Rural Aging Study (GRAS) is a longitudinal cohort of 21,645 community-dwelling older adults that were ≥65 years when they enrolled in a Medicare-managed health organization through the Geisinger Health System starting in 1994. The GRAS cohort resides in rural Pennsylvania and is a largely white, non-Hispanic population. Detailed information for the GRAS cohort has been described previously (9). In the present validation study, we recruited a cross-sectional subset of the GRAS cohort of community-dwelling participants aged ≥80 years during 2015 to 2016. Recruitment was completed in five steps: 1) initial screening of surviving GRAS participants ≥80 years of age (n=1,556); 2) contacting participants who did not have clinically diagnosed dementia based on ICD9 290.** and met inclusion criteria upon electronic medical record (EMR) review (n=1,201); 3) administering final screening and questionnaires among participants who consented to be enrolled in this study (n=174); 4) completing a phone interview to provide diet quality, functional status, and anthropometric data; and 5) completing three dietary recalls via telephone. After excluding participants who were missing both DST score and three-day dietary recalls (n=47), missing DST score only (n=3), and missing three-day dietary recalls only (n=2), the resulting sample of 122 participants was used in this analysis. Informed consent from study participants was obtained through telephone interview. Study approval was obtained from the Office of

Research Protections at The Pennsylvania State University and the Human Research Protection Program of the Geisinger Health Systems Institutional Review Board.

Assessment of DST score, HEI score, and covariates

Participants' diet quality was assessed using the DST survey which included twenty-five food- and behavior-specific questions associated with dietary intake, such as "How often do you usually eat fruit as a snack?", "How often do you usually eat whole grain breads?", and "How often do you usually eat candy or chocolate?". The DST score for each question was determined based on the response such as, never, less than once a week, 1 or 2 times a week, or 3 or more times a week, as detailed elsewhere (7). The total DST scores could range from 0 to 100 while 5 bonus points could be added for self-reported dietary supplement usage. Individuals who had a DST score lower than 60 were classified as "at risk", a DST score between 60 to 75 as "possibly at risk", and a DST score more than 75 as "not at risk" based upon our previous study examining the relationships between the DST categories and dietary recalls as well as nutritional biomarkers (7). Detailed information regarding DST development and validation has been described previously (6, 7).

Three 24-hour dietary recalls were collected via telephone by trained dietary interviewers from the Penn State Diet Assessment Center using the Nutrition Data System for Research (NDSR) software versions 2015 and 2016, developed by the Nutrition Coordinating Center (NCC), University of Minnesota, Minneapolis, MN. Final

calculations were completed using NDSR version 2016. The NDSR time-related database updates analytic data while maintaining nutrient profiles true to the version used for data collection. Dietary recall interviews were conducted on randomly selected non-consecutive days to include 1 weekend day and 2 weekdays, as recommended to ensure better estimates of usual intakes. Dietary components from the dietary recall were converted to cup or ounce equivalents per 1,000 kcal for HEI score calculation for most components except fatty acids, which were expressed as a ratio. HEI scores ranging from 0 (lowest) to 100 (highest) points with higher scores indicating preferable diet quality were calculated based on adequacy (total fruits, whole fruits, total vegetables, greens and beans, whole grains, dairy, total proteins, seafood and plant protein and fatty acid ratio) and moderation (refined grains, sodium, added sugars, and saturated fats) of the 13 dietary components listed in HEI-2015, as detailed elsewhere (10-12).

Self-reported age and sex were collected via telephone. Weight, height, and medical information including blood cholesterol, blood glucose, high density lipoprotein (HDL), low density lipoprotein (LDL), triacylglycerol, and history of disease conditions, such as diabetes, coronary artery disease, hypertension, liver disease, obstructive sleep apnea, depression, and osteoarthritis were obtained from electronic medical records based on ICD-9 diagnosis codes, current at the time of data collection. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$.

Statistical analyses

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). We calculated mean HEI scores and standard errors across three DST risk categories (at risk, possibly at risk, and not at risk) after adjusting for age and sex. We also presented results based on models in which we further adjusted for BMI, serum cholesterol, HDL, LDL, triacylglycerol, glucose as well as history of diabetes, coronary artery disease, hypertension, liver disease, obstructive sleep apnea, depression, and osteoarthritis recognizing the potential for over-adjustment. The correlation between the DST score and the HEI score were calculated by using Pearson correlation.

We generated a Bland-Altman plot to verify the relative validity of the DST as well as the extent of agreement between the DST and HEI scores by calculating the mean and difference of the Z-scores for DST and HEI scores. Standardized z-score, calculated as (observed value-mean value)/standard deviation, was utilized to evaluate the randomness due to the different score scaling of the DST and the HEI.

Results

Similar to the United States population, more older women were in the cohort than men (Table 3.1). No men were determined by the DST as "not at risk", and age was not associated with DST risk categories. No other significantly differences across DST risk categories were observed with regard to medical history or biomarkers of nutritional risk.

We observed a significant correlation between the DST score and the HEI score (age- and sex-adjusted r=0.68; p<0.001) (Table 3.2). Furthermore, the oldest old adults who were in the not-at-risk DST group had significantly higher HEI scores (adjusted means=79.6 ± 3.68) compared with individuals who are in the at-risk (adjusted means=51.2 ± 1.56) and the possibly-at-risk (adjusted means=66.3 ± 1.70) groups after adjusting for age and sex, known covariates of diet quality (p-difference<0.001) (Table 3.2). Further adjustment for other potential factors related to diet quality did not materially change this observed association.

In the Bland-Altman analysis, the points were scattered above and below zero, suggesting that there was no consistent bias of the DST versus the HEI scores (Figure 3.1).

Discussion

In this validation study, we observed that the DST scores were significantly correlated with the HEI scores calculated based on three-day dietary recalls across three statistical models. In addition, the oldest old adults who had higher diet quality assessed by the DST had significantly higher HEI scores compared with those who had lower diet quality. The Bland-Altman plot also supported the randomness and agreement between the DST and the HEI scores. These results suggest that the DST may be a valid diet quality screening tool relative to the HEI scores for the oldest old.

Experimental studies suggest that nutrition is one of the important environmental contributors to longevity among various organisms, such as yeast, *C elegans*, and mice (13). Although there are still limited human studies that have examined the associations between dietary quality, longevity, and successful aging, it is well-established that diet and nutritional status are strongly associated with risk of chronic disease among all ages, especially for older adults because of metabolic and functional declines associated with aging (14). Therefore, early detection and prevention of malnutrition through an effective dietary screening approach can be considered a key step in improving overall health conditions in older adults.

Older persons have higher risk of malnutrition due to age-related physiological changes, such as alteration in body composition, metabolic rate, chemosensory function, oral health, gastrointestinal conditions, and psychological and social issues that have the potential to negatively affect nutrient intake and absorption as well as metabolism (3, 14-

16). As suggested by studies conducted among older adults, adherence to good dietary habits is associated with lower risk of chronic diseases and mortality (17). Older persons are one of the fastest growing populations worldwide. As predicted by the United States Census, adults age 85 years and older are predicted to grow from 6 million in 2014 to approximately 20 million by 2060 (5). It is therefore important to identify strategies that target modifiable risk factors, especially diet quality, to improve health-related outcomes and quality of life for this population. A valid diet quality screening tool that can be easily administered through the telephone or in clinical settings will therefore be most useful to identify those at most risk.

One of the strengths of this analysis includes previous validation of the DST for use in other populations with consistent findings in relation to the HEI (18). The HEI measures overall diet quality reflecting adherence to Dietary Guidelines for Americans (11, 12). Given that diet quality as assessed by the HEI has been previously related to morbidity and mortality, these findings offer promise to those using the DST to examine the relationships between diet and health outcomes among the oldest old (19). Nevertheless, we acknowledge some limitations to the current study. Although the DST is valid and effective in assessing diet quality among the oldest old, we cannot estimate energy intake because limited food items are included in the DST. To address this concern, we examined the correlation between the DST score and the HEI score that were adjusted for total energy intake based on three-day dietary recalls and observed similar results. The HEI scores are based on estimates of usual intake of all foods and beverages consumed, while the DST scores are based on limited set of food questions that are

specific indicators of diet quality that may be, in part, unique to this population (7). Another limitation is the 30% observed exclusion rate for non-completion of the DST and/or three-day dietary recalls. The resulting sample size is relatively small but not atypical given the difficulties in collecting dietary information and survey questionnaires in a population of such advanced age. It should also be noted that since the DST was developed and validated in a cohort of older persons residing in a rural region of Pennsylvania with limited diversity, it may be necessary to modify it for application with different populations and regions.

In conclusion, the DST, to the best of our knowledge, is the first validated diet quality screening tool for use among the oldest old. The DST provides an easy to administer and simple approach to assess overall diet quality in this population, which is substantially less challenging and time consuming than multiple 24-hour recalls. Our findings also suggest the potential to use the DST to examine the associations between diet quality, nutritional status, and health outcomes, such as chronic disease and mortality, in the oldest old.

Take away points:

1. The dietary screening tool (DST) is the first diet quality screening tool that is validated to assess diet quality among the oldest old
2. The associations between diet quality and health consequences in the oldest old may be further examined by the use of the DST

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Table 3.1. Demographic and health-related characteristics of the oldest old cohort in the Geisinger Rural Aging Study (GRAS) by Dietary Screening Tool (DST) risk category (n=122)

	At risk group (DST score < 60)	**Possible-risk group (DST score 60-75)**	**Not-at-risk group (DST score > 75)**	*p*-value [4]
# of individuals	60	50	12	
Age (years) [1, 2]	85.8 ± 0.42	85.8 ± 0.46	87.3 ± 0.98	0.32
Sex (%)				0.0008
Men	58.3	42.0	0.0	
Women	41.7	58.0	100	
Body mass index (kg/m^2) [1, 3]	29.0 ± 0.61	27.9 ± 0.68	25.5 ± 1.45	0.08
Total cholesterol (mg/dL) [1, 3]	168 ± 4.67	174 ± 5.07	149 ± 10.5	0.09
Blood glucose (mg/dL) [1, 3]	121 ± 5.30	112 ± 5.87	106 ± 12.4	0.36
High density lipoprotein (mg/dL) [1, 3]	52.6 ± 2.16	56.7 ± 2.34	52.7 ± 4.87	0.41
Low density lipoprotein (mg/dL) [1, 3]	94.3 ± 4.07	94.8 ± 4.38	75.3 ± 9.46	0.16
Triglyceride (mg/dL) [1, 3]	115 ± 7.17	111 ± 7.79	90.9 ± 16.8	0.42

History of diabetes (%)	30.0	20.0	25.0	0.49
History of coronary artery disease (%)	50.0	38.0	41.7	0.44
History of hypertension (%)	85.0	86.0	75.0	0.63
History of liver disease (%)	1.7	0.00	0.00	0.59
History of obstructive sleep apnea (%)	13.3	16.0	16.7	0.91
History of depression (%)	3.3	4.0	0.00	0.78
History of osteoarthritis (%)	48.3	58.0	58.3	0.56

[1] Shown as mean ± standard error

[2] Adjusted for sex

[3] Adjusted for age and sex

[4] Differences across three categories

Table 3.2. Mean Healthy Eating Index (HEI) score[1] by the Dietary Screening Tool (DST) risk categories and correlation between the DST and HEI scores

	At risk group (DST score < 60)	Possible-risk group (DST score 60-75)	Not-at-risk group (DST score > 75)	*p*-value [2]	*r* (correlation) [3]
# of individuals	60	50	12		
Unadjusted	51.4 ± 1.54	66.1 ± 1.69	78.5 ± 3.45	<0.001	0.68
Age- and sex-adjusted	51.2 ± 1.56	66.3 ± 1.70	79.6 ± 3.68	<0.001	0.68
Multivariate-adjusted [4]	38.0 ± 7.63	52.1 ± 7.70	66.1 ± 8.61	<0.001	0.68

[1] Shown as mean ± standard error

[2] Difference in the HEI scores across three nutritional risk categories

[3] Correlation between the DST and the HEI scores (*p*-value<0.001 for all models)

[4] Adjusted for age, sex, body mass index (BMI), serum cholesterol, blood glucose, triglyceride, diabetes, coronary artery disease, hypertension, liver disease, obstructive sleep apnea, depression, and osteoarthritis status

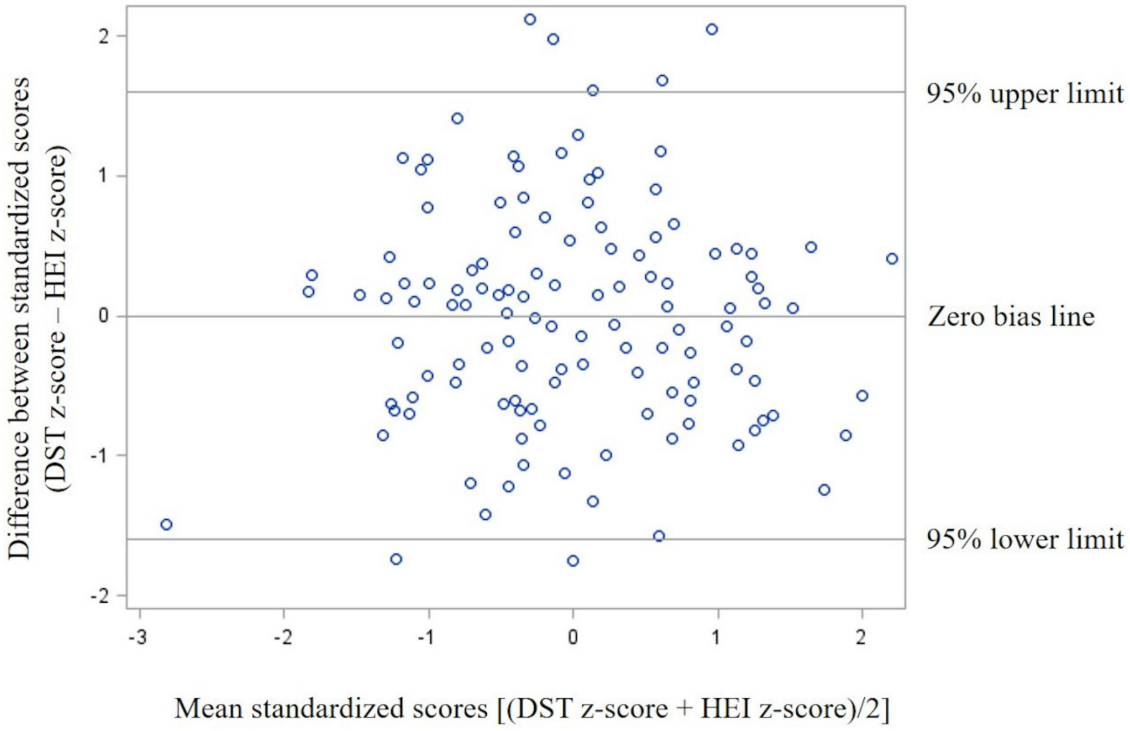

Figure 3.1. Bland-Altman plot evaluating relative validity of the Dietary Screening Tool (DST). The mean standardized z-scores of the DST and the Healthy Eating Index (HEI) were plotted against the difference between standardized z-scores from the DST and the HEI (n=122).

Appendices

Table 3.3. (Appendix 1) Mean Alternate Healthy Eating Index (AHEI)[1, 2] score by the Dietary Screening Tool (DST) risk categories and correlation between the DST and AHEI scores (n=122)

	At risk group (DST score<60)	Possible-risk group (DST score 60-75)	Not-at-risk group (DST score>75)	*p*-value [3]	*r* (correlation) [4]
# of individuals	60	50	12		
Unadjusted	47.9 ± 1.45	55.6 ± 1.59	64.1 ± 3.25	<0.001	0.44
Age- and sex-adjusted	47.8 ± 1.48	55.7 ± 1.61	65.1 ± 3.48	<0.001	0.44
Multivariate-adjusted [5]	37.2 ± 7.38	43.6 ± 7.44	54.1 ± 8.32	<0.001	0.44

[1] Shown as mean ± standard error

[2] AHEI scores were calculated using 11 dietary components with total possible score ranging from 0 (lowest) to 110 (highest). Detailed scoring method can be found in Chiuve SE, Fung TT, Rimm EB, et al. *J Nutr*. 2012;142(6):1009–1018.

[3] Difference in the AHEI scores across three nutritional risk categories

[4] Correlation between the DST and the AHEI scores (*p*-value<0.001 for all models)

[5] Adjusted for age, sex, body mass index (BMI), serum cholesterol, blood glucose, triglyceride, diabetes, coronary artery disease, hypertension, liver disease, obstructive sleep apnea, depression, and osteoarthritis status

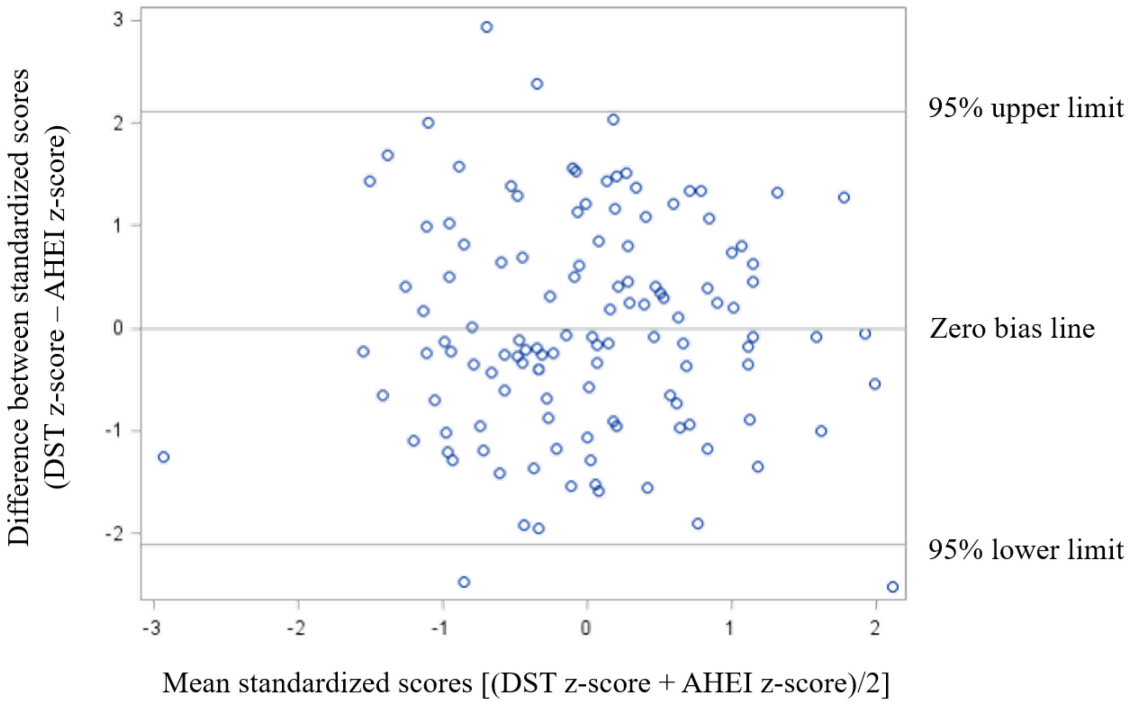

Figure 3.2. (Appendix 2) Bland-Altman plot evaluating relative validity of the Dietary Screening Tool (DST). The mean standardized z-scores of the DST and the Alternate Healthy Eating Index (AHEI) were plotted against the difference between standardized z-scores from the DST and the AHEI (n=122).

CHAPTER 4

DIET QUALITY IS ASSOCIATED WITH MORTALITY IN ADULTS AGED 80 YEARS AND OLDER: A PROSPECTIVE STUDY

A reprint is contained in the following pages.

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*Additional analyses conducted for this dissertation are placed in the end of this chapter as appendices.

Diet quality is associated with mortality in adults aged 80 years and older: a prospective study

Yi-Hsuan Liu, MS, RD[1], Xiang Gao, MD, PhD[1], Diane C. Mitchell, MS, RD[1], G. Craig Wood, MS[2], Christopher D. Still, DO, FACP, FTOS[2], and Gordon L. Jensen, MD, PhD[3]

[1] Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA;

[2] Obesity Institute, Geisinger Health System, Danville, PA;

[3] Larner College of Medicine, University of Vermont, Burlington, VT

Corresponding author

Xiang Gao, MD, PhD

Associate Professor

Department of Nutritional Sciences, The Pennsylvania State University

109 Chandlee Laboratory, University Park, PA 16802

Phone: 814-867-5959

Email: xxg14@psu.edu

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Abstract

Objectives: Diet quality has been associated with health outcomes and quality of life. However, the association between diet quality and mortality in older people, those aged 80 years and older, is under-studied. Therefore, we conducted a prospective study to examine whether better diet quality, assessed by a validated dietary screening tool (DST), was associated with lower mortality in those aged 80 years and older.

Methods: Our study included 1,990 participants (812 men and 1,178 women) with a mean age of 84.1 years at baseline (ranging from 80 to 102 years old) from the Geisinger Rural Aging Study (GRAS) longitudinal cohort in Pennsylvania. Baseline descriptive information was obtained in 2009 and the DST was administered via mailed survey. The DST is comprised of 25 food- and behavior-specific questions associated with dietary intake that generate a diet quality score ranging from 0 (lowest) to 100 (highest). Death was identified using electronic medical record (EMR) and the social security death index data. Hazard ratios (HRs) and 95% confidence intervals (CIs) across three diet quality categories were calculated by using cox proportional hazards models after adjusting for potential confounders.

Results: Over 8 years of follow-up (October 2009-February 2018), 931 deaths were documented. Higher diet quality was associated with lower mortality risk (p-trend=0.04). Participants with high diet quality (defined as DST scores >75) had significantly lower risk of mortality compared with those with low diet quality (defined as DST scores <60) after adjusting for potential risk factors (adjusted HR=0.76; 95% CI: 0.59-0.97).

Conclusion: Diet quality assessed by DST is significantly associated with risk of mortality in older adults aged 80 years and older in our prospective cohort. Our results indicate that nutrition may have an important role in healthy aging and more studies are needed to develop appropriate dietary recommendations for older persons.

Key words: diet quality; dietary pattern; mortality; healthy aging; mortality, older people

Introduction

Aging populations impact public health across the globe due to the associated burden of chronic disease. In the United States, the number of adults age 65 years and older are predicted to grow from 34 million in 2000 to 74 million in 2030 (1). Moreover, the number of individuals age 85 and older may grow from 6 million in 2014 to 20 million by 2060 (1). Promotion of healthy aging has therefore become a high priority.

Diet has long been considered one of the key contributors to healthy aging (2-5). In particular, the roles of dietary pattern and overall diet quality on health outcomes in older adults have been given increased attention since people consume foods instead of single nutrient components (6). Aging impacts physiological and social factors that may adversely affect diet quality (5). However, large prospective cohort studies of those aged 80 years and older that examine the relationships between diet quality and health outcomes like mortality are limited. One of the challenges in better understanding the associations between diet quality and health outcomes in older people aged 80 years and older is the limited availability of diet quality assessment methods validated for use in this population (2, 7).

In this context, we developed a dietary screening tool (DST), which was demonstrated to be valid and effective in measuring diet quality in older adults (8, 9) as well as those aged 80 years and older (10). In our previous study based on 2,995 older persons, we found that low diet quality, assessed by the DST, was associated with high risk of mortality during 3.1 years of mean follow-up (11). Here we present new results on

diet quality and mortality among approximately 2,000 participants aged 80 years and older over 8 years of follow-up.

Methods

Study population

The Geisinger Rural Aging Study (GRAS) was initiated in 1994 as a longitudinal cohort consisting of 21,645 community-dwelling older persons aged 65 years and over who enrolled in a Medicare-managed health organization through the Geisinger Health System at the time of entry. The majority of participants enrolled in the GRAS cohort are white and non-Hispanic. Rural central Pennsylvania has limited diversity. Detailed information regarding the GRAS cohort has been reported previously (12).

In October 2009, surveys requesting health status, demographic information, and the dietary screening tool (DST) were sent to 3,901 surviving GRAS participants, aged 80 years or older, by mail. Among participants who received mailed surveys, a total of 2,721 participants provided complete dietary surveys. After excluding those with unknown comorbidity disease status (data not available through medical claims and/or from the electronic medical records (EMR) or otherwise lost to follow up), the remaining 1,990 participants were followed through February 2018 (Figure 4.1). Supplementary Table 1 shows a comparison of basic characteristics between participants who were included in the follow-up and those who were not. Approval for implied consent through completion of the mailed surveys was obtained from the Office of Research Protections at The Pennsylvania State University and the Human Research Protection Program of the Geisinger Health Systems Institutional Review Board.

Assessment of diet quality

The DST survey questionnaire consisting of twenty-five food-based and behavior-based dietary questions was used to assess participants' diet quality via mailing in 2009. Example questions included in the DST are "How often do you usually eat fruit as a snack?", "How often do you usually eat whole grain breads?", and "How often do you usually eat candy or chocolate?" (Appendix 4.1). The total DST score could range from 0 to 100 with 5 bonus points for dietary supplement usage (9). The diet quality classification was then determined by the total DST score: <60 was categorized as low diet quality, 60 to 75 as moderate diet quality, and >75 as high diet quality, based upon our previously established and validated scoring calculation (9). More detailed information regarding DST development and validation has been described previously (8-10). In brief, the DST was developed in a subset of GRAS participants using detailed food intake and frequency analyses. The scoring algorithm classifying participants' diet quality was based on comprehensive dietary assessments as well as nutritional biomarkers (8, 9).

Assessment of death

Death was identified using both EMR and social security death index data. Participants' death data was obtained through February 7, 2018. Participants who survived through the last date of data extraction were censored during follow-up.

Assessment of covariates

Self-reported age, sex, race, weight, height, self- or proxy-reporting, smoking status, oral health status, and living arrangement were obtained using survey questionnaire data. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Participants' disease history and comorbidities were obtained from EMR data. Disease burden was determined based on the validated Charlson index of comorbidity (13). Participants' disease status was obtained from ICD-9 diagnosis codes identified in the EMR at the time of data collection.

Statistical analyses

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Demographic and other descriptive information were shown as means along with standard errors for continuous variables and percentages for categorical variables. Hazards ratios (HRs) and 95 % confidence intervals (CIs) across three diet quality categories (low, moderate, and higher quality) were formulated with the low quality group as reference using cox proportional hazards models after adjusting for potential confounders, including age, sex, BMI, self- or proxy-reporting, smoking status, living arrangement, oral health status, and Charlson index score at baseline. Trends in risk of mortality between diet quality categories were examined in cox proportional hazards models by assigning each group's median diet quality score to each participant based on their diet quality category. Possible interactions between diet quality and related confounders, including age, sex, BMI, and baseline Charlson index score, were tested by

adding a multiplicative term in the cox proportional hazard model with adjustment for the aforementioned covariates.

A total of five secondary analyses were conducted. Two secondary analyses were conducted to address the potential impact of medical conditions and self-reported oral health problems on diet quality by limiting the statistical analyses to 1,840 participants whose Charlson index score ≤5 and 1,871 participants who did not report self-perceived oral health problems. We also conducted two lag analyses by excluding participants who died within two (n=152) and four years (n=393) of follow-up to minimize potential reverse causality and overestimation. To determine whether diet quality categories assessed by the DST cutoffs could reflect proper classification of participants' diet quality, we conducted a secondary analysis using quintile classification based on their diet quality score. In a secondary analysis to address potential selection bias, we further included 720 out of 731 participants with available mortality information that were not part of the primary analysis due to unavailability of comorbidity disease status. For participants who were missing disease status, multiple imputation based on the Markov chain Monte Carlo (MCMC) method was utilized to replace missing baseline Charlson index score with plausible values (14). Categorial missing indicators were utilized to replace missing values for participants with missing covariates. Furthermore, we conducted a sensitivity analysis using an entry-age-adjusted age-scale model (left truncation) to address potential impact by the choice of time scale.

In order to better examine the relationship between continuous DST score and risk of mortality, we utilized a spline model analysis to test whether the relation is non-linear.

We examined the possibly non-linear relation between continuous DST score and mortality risk in older adults non-parametrically with restricted cubic splines (15, 16). Tests for non-linearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms (15).

Results

Within the 3,901 surviving GRAS participants, 1,911 of them did not return completed surveys, did not have available comorbidity disease status, or were otherwise lost to follow up (Figure 4.1). Participants who did not respond, provided incomplete surveys, or did not have available comorbidity disease status tended to be older and had higher mortality rate, compared with those who provided completed surveys and had comorbidity disease status (p-value<0.001 for all) (Supplementary Table 1).

Among the 1,990 participants included in the primary analysis, around 10.7% of them were categorized as having high diet quality, while 48.1% and 41.2% of them were considered having low and moderate diet quality, respectively. In particular, participants who had high diet quality were more likely to be women and never smokers (Table 4.1). There were no other significant differences observed in relation to age, race, BMI, or disease burden across three diet quality categories (Table 4.1).

Having higher diet quality was associated with lower mortality risk over 8 years of follow-up (adjusted HR=0.76, 95% CI: 0.59-0.97, p-trend=0.04) compared with having low diet quality after adjusting for age, sex, and other potential confounders (Table 4.2 and Supplementary Figure 1). This observed association between higher diet quality and lower risk of mortality remained significant after further excluding participants with baseline Charlson index score >5, who are known to have increased risk of mortality (adjusted HR=0.76, 95% CI: 0.59-0.99, p-trend=0.06) (Table 4.2). Similar associations were observed when participants with self-reported oral health problems

were excluded from the model (adjusted HR=0.72, 95% CI: 0.56, 0.94, *p*-trend=0.03) and with 2- and 4-year lag analyses (*p*-trend=0.02 for both lag-analyses) (Table 4.2). In addition, categorizing participants into quintiles according to their diet quality scores generated similar results (Supplementary Table 2). The significant trends between diet quality and risk of mortality were also observed in our secondary analysis when we further included individuals who were excluded due to not having available comorbidity disease status (Table 4.2 and Supplementary Table 3). Using an entry-age-adjusted age-scale model, we observed similar results (data not shown).

No significant interactions between diet quality and covariates, including age, sex, BMI, and baseline Charlson index score, were observed (*p*-interaction>0.10 for all).

Discussion

Our primary goal for this prospective study was to examine the association between diet quality and risk of mortality in older adults aged 80 years and over. By utilizing a validated dietary screening tool to assess overall diet quality, we observed that higher diet quality was associated with lower mortality risk over 8 years of follow-up. The observed association appeared not to be modified by other known risk factors (e.g., obesity and disease burden) for mortality. More importantly, our results suggest a potential linear relationship between higher diet quality score and lower risk of mortality. Taken together, these findings suggest the potential for lifestyle modification to reduce mortality risk in those aged 80 years and older. To the best of our knowledge, our study is the first observational study including the older adults aged ≥80 years that examined the relationship between diet quality and mortality.

Older persons, including those aged 80 years and older, are susceptible to age-related functional decline and environmental changes, such as alterations in metabolism, chewing problems, and changes in taste and smell, mobility, and living arrangements, which may in turn affect their access to food and nutrient intake (4, 5, 17). These age-related changes may lead to reduction in food intake and malnutrition in older persons that may in turn be associated with adverse health outcomes. In our study, the observed relationship between diet quality and mortality did not materially change after adjusting for age-related confounders such as chewing difficulty, pain in mouth, teeth, and gums, as well as living arrangement, which suggests that the association between high diet quality and lower risk of mortality is robust.

Results of our current study are also consistent with our earlier study including older persons age ≥65 years old that was of shorter duration (mean follow up of 3.1 years) with fewer incident mortalities and found that low diet quality was associated with higher mortality risk (11). Other observational studies have also found that adherence to a healthy diet, assessed by the healthy eating index (HEI), the Mediterranean diet score, and other indices, were associated with lower risk of mortality in pre-frail and frail older persons as well as older adults with sarcopenia (2, 18-22). However, some studies examining the relationships between dietary pattern, diet quality, and mortality among older persons in observational studies revealed inconclusive results (7, 22, 23). These outcomes may be associated with application of dietary screening tools that lack validity for the population being studied. Of note, prospective studies related to diet quality and health outcomes that only included older adults aged ≥80 years are very limited. Our findings should thus be considered preliminary and interpreted with caution.

According to 2015-2020 dietary guidelines for Americans, healthy eating patterns are defined as healthier food and beverage choices, appropriate amounts of varied and nutrient-dense foods, and reduction of added sugars, saturated fats and sodium intake (6). These revised dietary guidelines emphasize the importance of implementing overall healthy dietary patterns in order to help people meet nutritional requirements and maintain health status (6). Therefore, it is necessary to efficiently screen diet quality in older persons who are more likely to be malnourished in order to improve their health outcomes during the aging process. Dietary pattern and diet quality have been assessed by a priori and a posteriori methods (24). However, several methodological issues

confound dietary assessment in older persons including but not limited to feasibility, recall biases, efficacy, and cost. One of the strengths of our current study is the use of an effective and validated dietary screening tool, which is less memory-dependent and more time-efficient, to assess older persons' diet quality.

Older people account for approximately 23% of global burden of disease (25). Poor diet quality is associated with disease burden, mortality, and healthcare resource use (26). Adopting healthy dietary patterns may thus be an important and practical approach for older adults to meet their nutritional requirements to reduce risk of negative health consequences (27). By using a rapid dietary screening tool to effectively assess diet quality on a regular basis one can seek to guide improvement in the overall dietary pattern of older adults, especially those aged 80 years and older.

We used a validated dietary screening tool to identify diet quality in the older adults aged 80 years and over and to further relate participants' diet quality to risk of mortality in a well-established aging cohort, but there remain study limitations that must be recognized. High diet quality may be a marker reflecting overall better health condition that is not necessarily captured by potential confounders. Reverse causality may be a potential concern for a population at such advanced age, however, we observed similar associations between diet quality and mortality by excluding participants who died within two or four years of follow-up. Adjusting for the Charlson index of comorbidity score and excluding those with an index score ≥5 also generated similar results. Of note, high diet quality at baseline was associated with lower risk of mortality over 8 years of follow-up in our study, however, whether improving diet quality for

participants with low diet quality at baseline results in improved survival remains to be studied further. In addition, a notable limitation is that participants' energy intake cannot be obtained by the DST due to the scoring nature of this instrument (9). However, in our recent study that aimed to validate the DST against healthy eating index (HEI)-2015 based on three 24-hour dietary recalls, we observed that the DST score was significantly correlated with the HEI score among older adults aged ≥80 years (10). While the DST measures self-reported food behaviors, it has been shown that this tool can effectively identify older persons with nutritional risk in relation to nutritional biomarkers (9). Another limitation would be the potential bias resulted from self-reported smoking information. We observed that only 2.61% of participants reported themselves as a past or current smoker, which could underestimate the prevalence of smoking and introduce residual confounding. Furthermore, the DST was initially developed and later validated for older adults living in a rural area with higher homogeneity in race distribution and food habits. Therefore, the applicability of this tool to older persons with greater racial diversity residing in other geographic regions warrants further investigation.

In conclusion, we observed that higher diet quality, assessed by a validated dietary screening tool, is significantly associated with lower mortality risk in older adults aged ≥80 years in this prospective cohort with over 8 years of follow-up. Our findings suggest that adoption of healthy dietary patterns offers opportunity to promote healthy aging and reduced mortality.

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Table 4.1. Demographic and health-related characteristics of participants at baseline in the Geisinger Rural Aging Study (GRAS) by diet quality category (n=1,990)

	Diet quality			
	Low quality	**Moderate quality**	**High quality**	*p*-value
# of individuals	957	820	213	
Age (years) [1, 2]	84.0 ± 0.12	84.1 ± 0.13	83.9 ± 0.25	0.55
Sex (%)				<0.001
Men	47.3	37.0	26.3	
Women	52.7	63.1	73.7	
Race (%)				0.55
White	97.9	98.9	97.7	
Black or African American	0.00	0.12	0.00	
Asian	0.11	0.00	0.00	
American Indian or Alaska Native	0.11	0.00	0.00	
Unable to obtain	1.93	1.00	2.35	

Body mass index (BMI) (kg/m^2) [1, 3]	26.6 ± 0.16	26.6 ± 0.17	26.5 ± 0.33	0.87
Smoking status (%)				<0.001
Never smoker	91.6	94.0	99.1	
Past or current smoker	3.87	1.71	0.47	
Unknown	4.49	4.27	0.47	
Living arrangement (%)				0.29
House, apartment condominium, or mobile home	94.8	93.7	97.7	
Assisted-living apartment or boarding and care home	0.73	1.59	1.41	
Nursing home	0.31	0.24	0.00	
Other	0.52	0.49	0.00	
Unknown	3.66	4.02	0.94	
Difficulty chewing or swallowing (%)				0.10
Yes	4.60	4.15	1.41	
No	95.4	95.9	98.6	
Pain in mouth, teeth, or gums (%)				0.33

Yes	2.30	3.05	1.41	
No	97.7	97.0	98.6	
Dietary Screening Tool (DST) score [1, 3]	49.2 ± 0.20	66.7 ± 0.21	80.2 ± 0.42	<0.001
Charlson index score [1, 3]	2.16 ± 0.07	2.04 ± 0.08	1.88 ± 0.15	0.20

[1] Shown as mean ± standard error

[2] Adjusted for sex

[3] Adjusted for age and sex

Table 4.2. Association between diet quality and all-cause mortality in Geisinger Rural Aging Study (GRAS) over 8 years of follow-up (October 2009-February 2018) by diet quality category (n=1,990)

	Diet quality			
	Low quality	Moderate quality	High quality	*p*-trend
	Hazard Ratio (95% CI)			
Event/n	**485/957**	**371/820**	**75/213**	
Model 1 [1]	1 (reference)	0.86 (0.76, 0.99)	0.66 (0.52, 0.85)	<0.001
Model 2 [2]	1 (reference)	0.91 (0.80, 1.05)	0.74 (0.57, 0.94)	0.02
Model 3 [3]	1 (reference)	0.93 (0.81, 1.07)	0.76 (0.59, 0.97)	0.04
Sensitivity analyses				
Event/n	**423/877**	**330/763**	**67/200**	
Exclude individuals with Charlson index score >5 at baseline [3]	1 (reference)	0.94 (0.81, 1.09)	0.76 (0.59, 0.99)	0.06

Event/n	**448/898**	**345/766**	**70/207**	
Exclude individuals with self-reported oral problem(s) at baseline [3]	1 (reference)	0.93 (0.81, 1.08)	0.72 (0.56, 0.94)	0.03
Event/n	**409/881**	**311/760**	**59/197**	
Exclude individuals who died within two years of follow-up [3]	1 (reference)	0.92 (0.79, 1.07)	0.69 (0.52, 0.91)	0.02
Event/n	**278/750**	**222/671**	**38/176**	
Exclude individuals who died within four years of follow-up [3]	1 (reference)	0.95 (0.80, 1.14)	0.60 (0.42, 0.85)	0.02

[1] Adjusted for age and sex at baseline

[2] Adjusted for covariates listed in model 1 plus baseline body mass index (BMI), self- or proxy-reporting, smoking status, living arrangement, and oral health status

[3] Adjusted for covariates listed in model 2 plus baseline Charlson index score

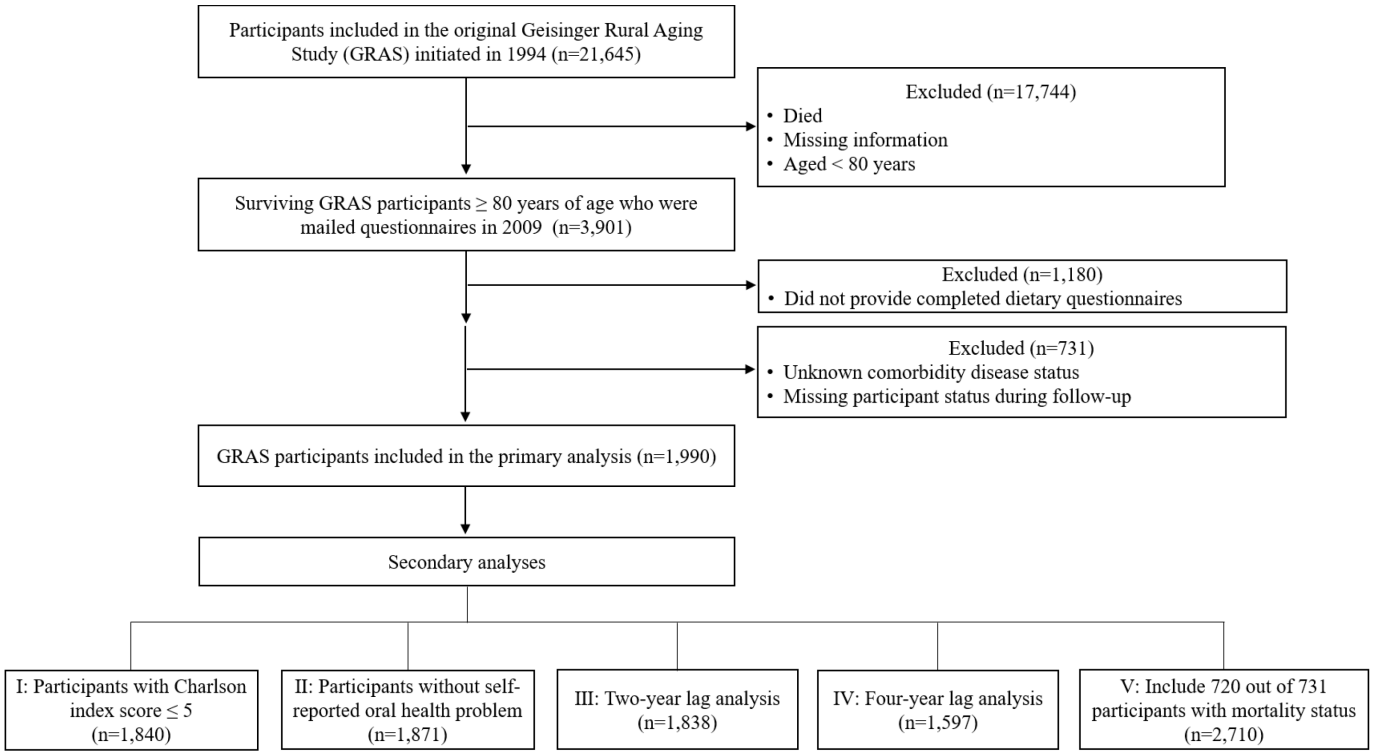

Figure 4.1. Flow chart of Geisinger Rural Aging Study (GRAS) participants. A total of 21,645 older adults were enrolled in GRAS longitudinal cohort starting from 1994. Surveys were mailed to 3,901 surviving GRAS participants in 2009. Among those who received surveys, 1,990 of them returned completed surveys and had available comorbidity disease status and thus were followed up through electronic medical records (EMR) forward.

Supplementary materials

Table 4.3. (Supplementary Table 1) Characteristics of cohort by survey completion and availability of comorbidity disease status in 2009

		Returned completed surveys and with comorbidity disease status in 2009		
		Yes	**No**	*p*-value
	# of individuals	1,990	1,911	
Age (years) [1, 2]		84.0 ± 0.09	84.9 ± 0.09	<0.001
Sex (%)				0.45
	Men	40.8	39.6	
	Women	59.2	60.4	
Patient status in 2018 (%)				<0.001
	Alive	53.2	39.6	
	Deceased	46.8	59.5	

Unknown	0.00	0.94	
Age- and sex- adjusted OR (95% CI) for mortality [3]	1 (reference)	1.51 (1.32, 1.72)	<0.001

[1] Shown as mean ± standard error

[2] Adjusted for sex

[3] OR: odds ratio; CI: confidence interval

Table 4.4. (Supplementary Table 2) Association between diet quality and all-cause mortality in Geisinger Rural Aging Study (GRAS) over 8 years of follow-up (October 2009-February 2018) by diet quality quintile (n=1,990)

	Diet quality					
	1st quintile (Lowest)	2nd quintile	3rd quintile	4th quintile	5th quintile (Highest)	*p*-trend
Event/n	**198/392**	**197/392**	**194/403**	**188/398**	**154/405**	
	Hazard Ratio (95% CI)					
Model 1 [1]	1 (reference)	1.03 (0.84, 1.25)	0.94 (0.77, 1.15)	0.92 (0.75, 1.12)	0.75 (0.61, 0.93)	0.005
Model 2 [2]	1 (reference)	0.98 (0.81, 1.19)	0.98 (0.80, 1.20)	0.94 (0.77, 1.15)	0.79 (0.64, 0.98)	0.04
Model 3 [3]	1 (reference)	0.96 (0.78, 1.17)	0.95 (0.78, 1.16)	0.96 (0.78, 1.18)	0.81 (0.65, 1.00)	0.08

[1] Adjusted for age and sex at baseline

[2] Adjusted for covariates listed in model 1 plus baseline body mass index (BMI), self- or proxy-reporting, smoking status, living arrangement, and oral health status

[3] Adjusted for covariates listed in model 2 plus baseline Charlson index score

Table 4.5. (Supplementary Table 3) Association between diet quality and all-cause mortality in Geisinger Rural Aging Study (GRAS) over 8 years of follow-up (October 2009-February 2018) including individuals who were excluded from primary analysis by diet quality category (n=2,710)

		Diet quality			
		Low quality	Moderate quality	High quality	*p*-trend
	Event/n	**656/1,265**	**529/1,136**	**117/309**	
			Hazard Ratio (95% CI)		
Model 1 [1]		1 (reference)	0.88 (0.78, 0.99)	0.69 (0.57, 0.85)	<0.001
Model 2 [2]		1 (reference)	0.91 (0.82, 1.03)	0.76 (0.62, 0.93)	0.007
Model 3 [3]		1 (reference)	0.92 (0.82, 1.04)	0.78 (0.64, 0.96)	0.03

[1] Adjusted for age and sex at baseline

[2] Adjusted for covariates listed in model 1 plus baseline body mass index (BMI), self- or proxy-reporting, smoking status, living arrangement, and oral health status

[3] Adjusted for covariates listed in model 2 plus imputed baseline Charlson index score

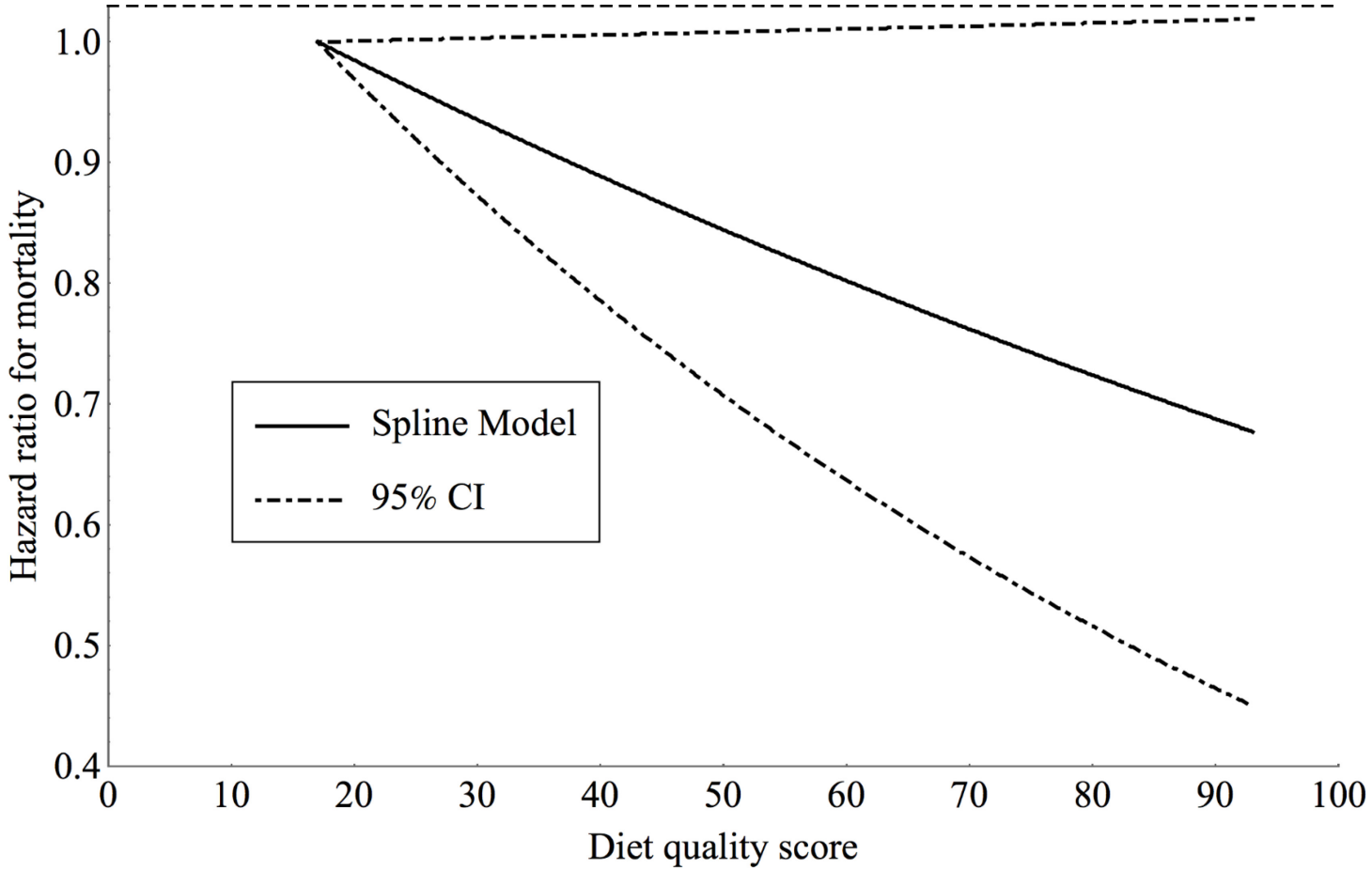

Figure 4.2. (Supplementary Figure 1) Spline model examining the relationship between continuous diet quality score and risk of mortality. (Adjusted hazard ratio=0.995; *p*-value=0.06) (n=1,990)

Dietary Screening Tool (DST) [1, 2]

How often do you usually eat fruit as a snack?

0 Never
2 Less than once a week
4 1 or 2 times a week
5 3 or more times a week

How often do you usually eat whole grain <u>breads</u>?

0 Never **or** less than once a week
3 1 or 2 times a week
5 3 or more times a week

How often do you usually eat whole grain <u>cereals</u>?

0 Never **or** less than once a week
3 1 or 2 times a week
5 3 or more times a week

How often do you usually eat candy or chocolate?

4 Never
3 Less than once a week
2 1 or 2 times a week
0 3 or more times a week

How often do you eat crackers, pretzels, chips, or popcorn?

4 Never
3 Less than once a week
2 1 or 2 times a week
0 3 or more times a week

How often do you eat cakes or pies?

4 Never
3 Less than once a week
2 1 or 2 times a week
0 3 or more times a week

How often do you eat cookies?

4 Never
3 Less than once a week
2 1 or 2 times a week
0 3 or more times a week

How often do you eat ice cream?

4 Never
3 Less than once a week
2 1 or 2 times a week
0 3 or more times a week

How often do you eat cold cuts, hot dogs, lunchmeats or deli meats?

5 Never **or** less than once a week
3 1 or 2 times a week
0 3 or more times a week

How often do you eat bacon or sausage?

5 Never **or** less than once a week
3 1 or 2 times a week
0 3 or more times a week

How often do you eat carrots, sweet potatoes, broccoli, or spinach?

0 Never
2 Less than once a week
6 1 or 2 times a week
8 3 or more times a week

How often do you eat fruit (not including juice)? Please include fresh, canned or frozen fruit?

0 Never **or** Less than once a week
2 1 or 2 times a week
4 3 to 5 times a week
5 Every day or almost every day

How often do you eat hot or cold breakfast cereal?

0 Never
1 Less than once a week
3 1 or 2 times a week
4 3 to 5 times a week
5 Every day or almost every day

How often do you drink some kind of juice at breakfast?

0 Never **or** Less than once a week
2 1 or 2 times a week
4 3 to 5 times a week
5 Every day or almost every day

How often do you eat chicken or turkey?

0 Never **or** less than once a week
3 1 or 2 times a week
5 More than 3 times a week

How often do you drink a glass of milk?

0 Never **or** Less than once a week
1 1 or 2 times a week
3 3 to 5 times a week
4 Every day or almost every day
5 More than once every day

Do you usually add butter or margarine to foods like bread, rolls, or biscuits?

0 Yes
1 No

Do you usually add fat (butter, margarine or oil) to potatoes and other vegetables?

0 Yes
1 No

Do you use gravy (when available) at meals?

0 Yes
1 No

Do you usually add sugar or honey to sweeten your coffee or tea?

0 Yes
1 No

Do you usually drink wine, beer or other alcoholic beverages?

0 Yes
1 No

How often do you eat fish or seafood that <u>IS NOT</u> fried?

0 Never
1 Less than once a week
3 Once a week
5 More than once a week

How many servings of milk, cheese, or yogurt do you usually have each DAY?

0 None
3 One
5 Two or more

How many different vegetable servings do you usually have at your main meal of the day?

0 None
1 One
5 Two
7 Three or more

Which of the following best describes your nutritional supplement use?

0 I don't use supplements
0 I use supplements other than vitamins and mineral
5 I use a multivitamin/mineral preparation (e.g. Centrum)

[1] Responses to questions were scored according to the bolded score values listed for each answer. The bolded score values were not presented on the DST when it was completed by the participants.
[2] The total DST score could range from 0 to 100 with 5 bonus points for dietary supplement usage (the last question).

Appendices

Table 4.6. (Appendix 1) Association between diet quality and all-cause mortality in Geisinger Rural Aging Study (GRAS) over 8 years of follow-up (October 2009-February 2018) by diet quality category (n=1,990): including educational level as a covariate

	Diet quality			
	Low quality	Moderate quality	High quality	*p*-trend
	Hazard Ratio (95% CI)			
Event/n	**485/957**	**371/820**	**75/213**	
Model 1 [1]	1 (reference)	0.86 (0.76, 0.99)	0.66 (0.52, 0.85)	<0.001
Model 2 [2]	1 (reference)	0.92 (0.80, 1.05)	0.75 (0.58, 0.96)	0.03
Model 3 [3]	1 (reference)	0.93 (0.81, 1.07)	0.77 (0.60, 0.98)	0.048
Sensitivity analyses				
Event/n	**423/877**	**330/763**	**67/200**	
Exclude individuals with Charlson index score >5 at baseline [3]	1 (reference)	0.95 (0.82, 1.09)	0.78 (0.60, 1.01)	0.09

Event/n	**448/898**	**345/766**	**70/207**	
Exclude individuals with self-reported oral problem(s) at baseline [3]	1 (reference)	0.94 (0.81, 1.08)	0.73 (0.57, 0.95)	0.04
Event/n	**409/881**	**311/760**	**59/197**	
Exclude individuals who died within two years of follow-up [3]	1 (reference)	0.93 (0.80, 1.08)	0.70 (0.53, 0.93)	0.02
Event/n	**278/750**	**222/671**	**38/176**	
Exclude individuals who died within four years of follow-up [3]	1 (reference)	0.96 (0.80, 1.15)	0.61 (0.43, 0.86)	0.03

[1] Adjusted for age and sex at baseline

[2] Adjusted for covariates listed in model 1 plus baseline body mass index (BMI), self- or proxy-reporting, smoking status, living arrangement, oral health status, and educational level

[3] Adjusted for covariates listed in model 2 plus baseline Charlson index score

Table 4.7. (Appendix 2) Association between individual Dietary Screening Tool (DST) component score and risk of mortality in Geisinger Rural Aging Study (GRAS) (n=1,990)

DST component	Hazard Ratio (95% CI) [1, 2]	*p*-value
1) How often do you usually eat fruit as a snack?	1.01 (0.96, 1.07)	0.60
2) How often do you usually eat whole grain breads?	0.97 (0.94, 1.00)	0.07
3) How often do you usually eat whole grain cereals?	0.97 (0.94, 1.01)	0.10
4) How often do you usually eat candy or chocolate?	0.98 (0.93, 1.03)	0.40
5) How often do you eat crackers, pretzels, chips, or popcorn?	1.04 (0.99, 1.10)	0.10
6) How often do you eat cakes or pies?	0.99 (0.93, 1.05)	0.74
7) How often do you eat cookies?	0.95 (0.90, 1.00)	0.07
8) How often do you eat ice cream?	0.97 (0.92, 1.03)	0.35
9) How often do you eat cold cuts, hot dogs, lunchmeats or deli meats?	0.99 (0.95, 1.02)	0.41
10) How often do you eat bacon or sausage?	1.01 (0.94, 1.07)	0.84
11) How often do you eat carrots, sweet potatoes, broccoli, or spinach?	0.97 (0.95, 0.998)	0.04

12) How often do you eat fruit (not including juice)? Please include fresh, canned or frozen fruit	1.01 (0.97, 1.05)	0.57
13) How often do you eat hot or cold breakfast cereal?	0.96 (0.92, 1.00)	0.06
14) How often do you drink some kind of juice at breakfast?	1.01 (0.98, 1.04)	0.41
15) How often do you eat chicken or turkey?	0.98 (0.95, 1.02)	0.40
16) How often do you drink a glass of milk?	0.99 (0.95, 1.03)	0.60
17) Do you usually add butter or margarine to foods like bread, rolls, or biscuits?	0.97 (0.79, 1.19)	0.77
18) Do you usually add fat (butter, margarine or oil) to potatoes and other vegetables?	0.95 (0.81, 1.11)	0.49
19) Do you use gravy (when available) at meals?	0.94 (0.80, 1.10)	0.41
20) Do you usually add sugar or honey to sweeten your coffee or tea?	0.94 (0.82, 1.08)	0.37
21) Do you usually drink wine, beer or other alcoholic beverages?	0.97 (0.92, 1.02)	0.19
22) How often do you eat fish or seafood that IS NOT fried?	0.97 (0.93, 1.01)	0.16
23) How many servings of milk, cheese, or yogurt do you usually have each DAY?	1.23 (1.00, 1.50)	0.05
24) How many different vegetable servings do you usually have at your main meal of the day?	1.00 (0.97, 1.03)	0.91

25) Which of the following best describes your nutritional supplement use?	1.01 (0.98, 1.04)	0.48

[1] Adjusted for age, sex, baseline body mass index (BMI), source of information, smoking status, living arrangement, oral health status, baseline Charlson index score, and educational level

[2] The association between one point increase in the DST component score and risk of mortality

CHAPTER 5

DIET QUALITY AND RISK OF PARKINSON DISEASE: A PROSPECTIVE STUDY AND A META-ANALYSIS

Diet quality and risk of Parkinson disease: a prospective study and a meta-analysis

Yi-Hsuan Liu, MS, RD[1], Gordon L. Jensen, MD, PhD[2], Muzi Na, PhD[1], Diane C. Mitchell, MS, RD[1], G. Craig Wood, MS[3], Christopher D. Still, DO, FACP, FTOS[3], and Xiang Gao, MD, PhD[1]

[1] Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA;

[2] Larner College of Medicine, University of Vermont, Burlington, VT;

[3] Obesity Institute, Geisinger Health System, Danville, PA

Corresponding author

Xiang Gao, MD, PhD

Associate Professor

Department of Nutritional Sciences, The Pennsylvania State University

109 Chandlee Laboratory, University Park, PA 16802

Phone: 814-867-5959

Email: xxg14@psu.edu

Short running head: Diet quality and Parkinson disease

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Abstract

Objectives: Several dietary components have been shown to be neuroprotective against risk of neurodegeneration. We thus examined the associations between diet quality and risk of Parkinson disease in a prospective cohort study and a meta-analysis.

Methods: Included in the cohort study were 3,653 participants (1,519 men and 2,134 women; mean age: 81.5 years) in the Geisinger Rural Aging Study longitudinal cohort in Pennsylvania. Diet quality was assessed using a validated dietary screening tool containing 25 food- and behavior-specific questions in 2009. Potential Parkinson cases were identified using electronic health records based on ICD9 (332.*), ICD10 (G20), and Parkinson-related treatments. Incident Parkinson cases were defined as being diagnosed at least 1 year after completing diet quality assessment and receiving Parkinson-related medication treatments. Hazard ratios (HRs) and 95% confidence intervals (CIs) across diet quality tertiles were calculated using Cox proportional hazards models after adjusting for age, sex, race, educational level, smoking, oral health, obesity and living arrangement. We further performed a meta-analysis by pooling our study with four published papers on this topic. Random-effects model was utilized to calculate the pooled risk ratios and 95% confidence intervals (CIs).

Results: During a mean of 6.94 years of follow-up, 47 incident Parkinson cases were documented. Having high diet quality at baseline was associated with lower Parkinson disease risk (*p*-trend=0.02). The adjusted HR was 0.39 (95% CI: 0.17-0.89) for the highest vs the lowest diet quality tertiles. The meta-analysis including 140,617 individuals also showed that adherence to high diet quality or a healthy dietary pattern

was associated with lower risk of Parkinson disease (pooled risk ratio=0.64; 95% CI: 0.49-0.83).

Conclusion: Having high diet quality or a healthy dietary pattern was associated with lower future risk of Parkinson disease.

Key words: diet quality; Parkinson disease; prospective study; meta-analysis

Introduction

Parkinson disease is the second most common neurodegenerative disease. With a rising trend of prevalence, more than one million individuals in the United States may suffer from Parkinson disease by 2030 (1). Motor symptoms, such as tremor, rigidity, bradykinesia, are commonly observed in individuals with Parkinson disease (2). Growing evidence also suggests that a wide range of non-motor symptoms, including cognitive impairment, dementia, depression, constipation, and sleep disorders, can also occur in individuals with Parkinson disease (3).

A number of observational studies have examined the association between individual dietary component and risk of Parkinson disease (4, 5), however, observational studies investigating the role of overall diet quality (dietary pattern) on the pathogenesis of Parkinson disease are limited. Understanding the impact of overall diet quality may provide better insights in relation to diet and Parkinson disease because synergistic effects of food components and potential nutrient interactions in diets can also be considered (6, 7).

In this study, we aimed to prospectively examine the association between overall diet quality and risk of incident Parkinson disease in a longitudinal cohort of 3,653 community-dwelling older adults who were not diagnosed with Parkinson disease at baseline. Diet quality was assessed by a validated Dietary Screening Tool (DST). In our previous validation analysis including 122 oldest old aged 80 years and over, significant correlation between the DST score and the Healthy Eating Index (HEI)-2015 score was

observed (8). Participants categorized as having high diet quality by the DST also had significantly higher HEI-2015 score (8). In addition, our previous study including 204 older adults aged 65 years and older showed that participants categorized as having high diet quality by the DST had better overall biochemical indicators of nutritional status compared with those being categorized as having low diet quality (9). The evidence suggests that the DST is a valid measurement of diet quality among older adults and oldest old (8, 9). We also performed a meta-analysis of observational studies to summarize current evidence on diet quality and the development of Parkinson disease. We hypothesized that having high diet quality or adherence to a healthy dietary pattern would be associated with lower risk of developing Parkinson disease.

Methods

Cohort analysis

Study population

The Geisinger Rural Aging Study (GRAS) originated in 1994 as a longitudinal cohort including 21,645 community-dwelling older persons aged 65 years and over in rural Pennsylvania with limited diversity in race and lifestyle factors. Participants who enrolled in a Medicare-managed health organization through the Geisinger Health System at the time of entry were eligible. Detailed information regarding the GRAS cohort has been reported previously (10).

In October 2009 (baseline of this current study), mailed surveys were sent to 5,939 surviving GRAS participants to obtain demographic and descriptive information and diet quality. A total of 4,020 participants returned completed surveys and diet quality assessment. After excluding participants who had prevalent Parkinson disease at baseline or lost to follow up, 3,653 participants were included in the current analysis (Figure 5.1).

Standard protocol approvals, registrations, and patient consent

Approval for implied consent through completion of the mailed surveys was obtained from the Office of Research Protections at The Pennsylvania State University and the Human Research Protection Program of the Geisinger Health Systems Institutional Review Board.

Assessment of diet quality

Diet quality was assessed at baseline in 2009 using the mailed Dietary Screening Tool (DST) survey questionnaire that included twenty-five food- and behavior-based dietary questions. Some sample questions in the DST are "How often do you usually eat whole grain breads?" and "How often do you usually eat candy or chocolate?". The total DST score could range from 0 to 100 and 5 bonus points would be scored for dietary supplement usage (9). Participants' diet quality categories were determined based on tertiles of the DST score. More detailed information regarding DST development and validation in older persons has been described previously (8, 9, 11).

Assessment of incident Parkinson disease cases

Parkinson disease cases were identified using Electronic Health Record (EHR) based on ICD9 (332.*) and later verified by ICD-10-CM code G20 through September 9, 2019. Incident Parkinson disease cases were defined as being diagnosed at least 1 year after completing diet quality assessment and receiving Parkinson-related medication treatment(s), including medication containing carbidopa/levodopa (Sinemet, Parcopa, Stalevo, Duodopa), ropinirole (Requip), pramipexole (Mirapex), rasagiline (Azilect), pergolide (Permax), rotigotine (Neupro), entacapone (Comtan), selegiline (Eldepryl, Zelapar), carbidopa (Lydosyn), or amantadine (Symmetrel).

Assessment of covariates

Self-reported demographic and descriptive variables, including age, sex, race, weight, height, educational level, self- or proxy-reporting, smoking status, oral health status, living status (live alone or with family members) and living arrangement (at home, skilled nursing, or other facility), were collected using the mailed survey questionnaire at baseline. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$.

Statistical analyses

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Characteristic and demographic variables were presented as means along with standard errors for continuous variables and percentages for categorical variables. Hazards ratios (HRs) and 95% confidence intervals (CIs) across diet quality tertiles were calculated with the lowest tertile as a reference in Cox proportional hazards models after adjusting for potential confounders, including age, sex, race, BMI, educational level, self- or proxy-reporting, smoking status, oral health status, living status, and living arrangement at baseline. The proportional assumption was tested by including covariate by time interaction effects into the model (p>0.05 for all) (12). We examined trends in risk of incident Parkinson disease between diet quality tertile in Cox proportional hazards models by assigning each tertile's median diet quality score to each participant based on their corresponding diet quality tertile. Possible interactions between diet quality and related covariates, including age, sex, BMI, and educational level, were tested by adding

a multiplicative term in the Cox proportional hazards model after adjusting for the aforementioned covariates.

Four sensitivity analyses were conducted to test the robustness of our results: 1) restricting the statistical analyses to 3,463 participants without any self-reported oral health problem to avoid potential impact of self-reported oral health problem(s) on diet quality as our previous study found poor oral health to be strongly associated with poor diet quality (13); 2) excluding participants who were diagnosed with Parkinson disease within two years of follow-up (n=11) to address potential reverse causality; 3) excluding participants who were diagnosed with Parkinson disease within two years of follow-up and with self-reported oral health problem(s) (n=201); and 4) further including 31 participants who were diagnosed with incident Parkinson disease while not receiving Parkinson-related treatment as cases in the model to determine whether incident Parkinson cases were underestimated by defining cases as being diagnosed and receiving medication treatment.

Meta-analysis

Search strategy

We systematically searched in the PubMed, Web of Science, and Cumulative Index for Nursing and Allied Health (CINAHL) databases starting from January 1, 1981 up to November 6, 2019. Search terms related to diet quality, dietary pattern, and Parkinson disease in controlled vocabulary (in PubMed and CINAHL) as well as text

were used. Studies assessing either diet quality or dietary pattern were included in order to provide a comprehensive picture of diet assessed by *a priori* and *a posteriori* methods in relation to Parkinson disease. Detailed search words for the three databases with results can be found in Supplementary Table 1.

Eligibility criteria

Study selection was completed using the inclusion and exclusion criteria listed in Supplementary Table 2. Observational studies, including prospective, retrospective, and case-control studies, written in English as a primary research article in a peer-reviewed journal were included. Studies that assessed overall dietary patterns or diet quality using either an *a priori* or *a posteriori* approach were eligible. Ineligible studies included those that focused on a single nutrient or selected dietary components. Additionally, eligible studies must have outcome(s) of clinically diagnosed Parkinson disease.

Study selection process, data extraction, and quality assessment

Study selection and coding process were conducted and managed using Rayyan online software by one reviewer (YL) and verified by a second reviewer (MN). Data extraction for each included study was conducted by one reviewer (YL) and verified the other reviewer (MN). Extracted data included study characteristics, cohort, characteristics of participants, covariates, dietary assessment, outcome assessment, statistical methods, and primary results. Quality of all included studies was assessed using Newcastle-Ottawa

Scale stars (14). Possible stars for quality assessment ranged from 0 to 9 stars with 7 stars or higher representing good study quality (14). The results of study quality assessment are shown in Table 3.

Statistical analyses

Statistical analyses were carried out using Stata/SE software version 15.1 (StataCorp, College Station, TX) to pool results from all included studies. Pooled risk ratios and 95% CIs between two dietary pattern scores or diet quality categories (the highest versus the lowest) were calculated with the lowest dietary pattern score or diet quality group as reference using random effects models in generic inverse variance method. For a study with separate results for men and women, two results were pooled as one risk ratio and included in the models (15). Heterogeneity among studies was examined by Q statistics and I^2 index with 25%, 50%, and 75% representing low, moderate, and high heterogeneity (16).

Results

Cohort analysis

After a mean of 6.94 years of follow-up, 47 incident Parkinson cases were documented. Participants with better diet quality were more likely to be women and never smoker, have higher educational level, and live with family members (Table 5.1). We did not observe other significant differences across diet quality tertiles in other demographic and descriptive variables (Table 5.1).

Having high diet quality was associated with lower risk of incident Parkinson disease during a mean of 6.94 years of follow-up (adjusted HR=0.39 comparing two extreme tertiles; 95% CI: 0.17-0.89; *p*-trend=0.02) after adjusting for potential confounders (Table 5.2). The sensitivity analyses excluding participants who had self-reported oral health problem(s) generated similar results (adjusted HR=0.39; 95% CI: 0.17-0.90; *p*-trend=0.02) (Table 5.2). Similar trends between diet quality and risk of Parkinson disease were also observed in the sensitivity analyses excluding participants who were diagnosed within two years of follow up plus with self-reported oral health problem(s) (*p*-trend=0.05) and the sensitivity analysis further including Parkinson cases without medication treatment, however, the association lost significance (*p*-trend=0.16) (Table 5.2).

Increased intake frequency of fruit, whole grain cereals, hot or cold breakfast cereals, and juice at breakfast was associated with lower risk of Parkinson disease (*p*-value<0.05 for all), however, we did not observe significant association between other

DST components and risk of Parkinson disease (Supplementary Table 3). No significant interactions between diet quality and potential confounders, including age, sex, BMI, and educational level, were observed (*p*-interaction>0.05 for all) (data not shown).

Meta-analysis

A total of 163 studies were identified based on our search strategy and 4 studies (5 study populations) met our inclusion criteria (Supplementary Figure 1). Among the 4 studies included, 2 studies utilized hypothesis-driven *a priori* diet assessments (15, 17), 1 study assessed dietary pattern/diet quality using data-driven *a posteriori* approaches (18), and 1 study utilized both *a priori* and *a posteriori* assessments (19). In addition, 2 were prospective studies with follow-up period ranging from 16 to 41 years (15, 19) and 2 were case-control studies (17, 18). Within the 4 studies identified, 3 of them showed a statistically significant inverse associations between dietary pattern and risk of Parkinson disease (Table 5.3).

A significant association between having high diet quality or high dietary pattern scores and lower risk of Parkinson disease compared with those with low diet quality or low dietary pattern scores was observed in our meta-analysis (pooled risk ratio=0.64; 95% CI: 0.49-0.83) (Figure 5.2).

Discussion

In our prospective study conducted in over 3600 older adults living in a rural region, we observed that having high diet quality, as assessed by a validated diet quality screening tool, was associated with lower future risk of Parkinson disease. This association was independent of several potential confounders, including age, sex, BMI, and education level. Similarly, our meta-analysis of 6 study populations revealed that adherence to a healthy dietary pattern or having high diet quality was associated with lower odds of Parkinson disease. Our results suggest that a healthy diet may be a potential modifiable lifestyle factor that may delay or prevent the onset of Parkinson disease. To the best of our knowledge, our study is the first meta-analysis investigating the relationship between overall diet quality and risk of Parkinson disease.

Parkinson disease is a complex and multifactorial disease which could be related to genetic, environmental, and lifestyle factors. In particular, a recent study examining the heritability of Parkinson disease showed the overall heritability to be only 0.27, strengthening the potential importance of environmental and lifestyle factors in the development of Parkinson disease (20). Diet has gained increased attention as dietary components and dietary patterns are modifiable lifestyle factors which could positively or negatively impact Parkinson disease pathogenesis (21). Dietary factors have emerged as one of the main determining factors in the metabolic health of gut microbiota, which may in turn regulate the progression of Parkinson disease (21). Some vitamins and antioxidants, for example, vitamin B6, vitamin E, flavonoids, and magnesium were shown to be inversely associated with risk of Parkinson disease in some (4, 5, 22-24) but

not all published studies (25, 26). In contrast, dietary components commonly observed in the Western diet, such as high saturated fats and low dietary fiber were related to higher risk of Parkinson disease in a recent review (21). Adherence to a healthy dietary pattern, characterized as high consumption of fruits and vegetables, polyunsaturated fatty acids, plant-based proteins and low intakes of red meat and saturated fats may therefore be associated with lower risk of Parkinson disease (21).

Known factors that are associated with altered risk of Parkinson disease include cigarette smoking, socioeconomic status, and sex (27). Several studies suggested that cigarette smokers have lower risk of developing Parkinson disease (28, 29). In addition, some studies suggested that people with low socioeconomic status or low work complexity had lower risk of Parkinson disease compared with individuals with high socioeconomic status or high work complexity (30, 31). Studies also suggested that sex is one of the key factors in Parkinson disease as women have lower risk of disease development compared with men (32, 33). In our prospective study, we also observed that being a smoker, having lower educational level, or being female may be associated with lower risk of developing Parkinson disease in our multivariate model (data not shown). However, the observed inverse association between overall diet quality and low Parkinson disease risk was not significantly modified by these factors.

To date, the pathogenesis of developing Parkinson disease and associated metabolic changes before disease onset remain unclear. However, some studies suggested that non-motor symptoms (i.e., prodromal Parkinson symptoms), such as anxiety or constipation, could have more than 20 years of preclinical phase while neuropathology

might have 5 to 6 years of preclinical period (34). Reverse causality could thus be another potential interpretation for our findings. Because of long pre-clinical stage prior to being diagnosed, individuals with underlying prodromal Parkinson symptoms may have already changed their dietary habits. Although our 2-year lag analysis generated a similar association between high diet quality and lower risk of Parkinson disease, we still cannot totally exclude the possibility of reverse causality. Alternately, these results could suggest that healthy diet quality might be associated with lower risk of conversion from prodromal to clinical Parkinson disease.

There are some additional limitations that need to be carefully considered when interpreting our study results. First, in our prospective study, we were unable to estimate participants' energy consumption because of the design and limited food items included in the DST. Moreover, only 3.4% of participants reported a past- or current smoking habit. Smoking may well be under-reported and so result in potential residual confounding. Interestingly, smoking behavior has also been associated with poor diet quality (35). We may thus underestimate the true diet-Parkinson relationship. Generalizability of findings from our cohort needs to be further studied due to limited diversity in the GRAS cohort with most of participants being non-Hispanic white. However, similar association between diet quality and risk of Parkinson disease was observed in the meta-analysis, in which studies with different study designs and populations were included. Although we conducted a very comprehensive systematic literature search for our meta-analysis, only 6 cohorts were selected for inclusion. The small number of studies included have limited our ability to further perform subgroup

analyses to examine the potential impact of heterogeneity across cohorts. Various dietary assessments (i.e. *a priori* and *a posteriori*) were utilized in the selected individual studies which may in turn impact interpretation of results in our meta-analysis (36). However, similar characteristics, for example, increased consumption of fruits and vegetables and decreased consumption of red meat and saturated fats, are likely shared in most of the identified healthy dietary pattern or high-quality diets.

In summary, results from our prospective study and meta-analysis suggest that having high diet quality or adherence to a healthy dietary pattern are associated with lower risk of Parkinson disease. More observational studies with larger sample size and longer follow-up are needed to better understand the temporal relationship between dietary pattern and the development of Parkinson disease.

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Table 5.1. Demographic and characteristic information of participants at baseline in the Geisinger Rural Aging Study (GRAS) by diet quality tertile (n=3,653)

		Diet quality			
		Lowest tertile	Medium tertile	Highest tertile	*p*-value
	# of individuals	1,204	1,235	1,214	
Age (years) [1, 2]		84.0 ± 0.13	81.5 ± 0.12	81.5 ± 0.13	0.94
Sex (%)					<0.001
	Men	48.8	43.6	32.5	
	Women	51.3	56.4	67.6	
Race (%)					0.37
	White	94.3	94.0	95.7	
	Other	1.08	1.21	0.74	
	Unable to obtain	4.65	4.78	3.54	
Body mass index (BMI) (kg/m^2) [1, 3]		27.3 ± 0.15	27.5 ± 0.15	27.2 ± 0.15	0.42
Educational level (%)					<0.001

Below college degree	84.1	76.9	72.9	
College degree	8.22	12.2	16.4	
Graduate degree	1.91	5.02	6.01	
Unknown	5.73	5.83	4.70	
Smoking status (%)				<0.001
Never smoker	89.1	91.6	94.7	
Past or current smoker	5.65	3.00	1.57	
Unknown	5.23	5.43	3.71	
Living status (%)				<0.001
Live alone	63.5	63.6	56.7	
With spouse, son/daughter, or other family member	32.3	31.1	39.9	
Unknown	4.15	5.34	3.46	
Living arrangement (%)				0.46
House, apartment condominium, or mobile home	94.0	92.6	94.3	
Assisted-living apartment or care/nursing home	1.58	1.86	1.65	

Unknown	4.40	5.51	4.04	
Self-reported oral health problem (%)				0.67
Yes	5.65	5.10	4.86	
No	94.4	94.9	95.1	
Dietary Screening Tool (DST) score [1, 3]	46.0 ± 0.15	60.5 ± 0.15	73.9 ± 0.16	<0.001

[1] Shown as mean ± standard error

[2] Adjusted for sex

[3] Adjusted for age and sex

Table 5.2. Association between diet quality and incident Parkinson disease in Geisinger Rural Aging Study (GRAS) over 6.94 years of follow-up by diet quality tertile (n=3,653)

	Diet quality			
	Lowest tertile	Medium tertile	Highest tertile	*p*-trend
	Hazard Ratio (95% CI)			
Event/n	**24/1,204**	**15/1,235**	**8/1,214**	
Model 1 [1]	1 (reference)	0.61 (0.32, 1.17)	0.36 (0.16, 0.80)	0.01
Model 2 [2]	1 (reference)	0.64 (0.33, 1.24)	0.39 (0.17, 0.89)	0.02
Event/n	**23/1,136**	**13/1,172**	**8/1,155**	
Exclude individuals with self-reported oral problem(s) at baseline [3]	1 (reference)	0.56 (0.28, 1.12)	0.39 (0.17, 0.90)	0.02
Event/n	**18/1,198**	**12/1,232**	**6/1,212**	
Exclude individuals who were diagnosed within 2 years of follow-up [2]	1 (reference)	0.70 (0.33, 1.49)	0.40 (0.16, 1.05)	0.06

Event/n	**17/1,130**	**10/1,169**	**6/1,153**	
Exclude individuals who were diagnosed within 2 years of follow-up and with self-reported oral problem(s) at baseline [3]	1 (reference)	0.59 (0.27, 1.32)	0.40 (0.16, 1.05)	0.05
Event/n	**32/1,204**	**28/1,235**	**18/1,214**	
Include Parkinson participants without medication treatment as cases [2]	1 (reference)	0.90 (0.54, 1.52)	0.65 (0.36, 1.17)	0.16

[1] Adjusted for age and sex at baseline

[2] Adjusted for covariates listed in model 1 plus race, baseline body mass index (BMI), educational level, self- or proxy-reporting, smoking status, living status, living arrangement, and oral health status

[3] Adjusted for covariates listed in model 1 plus race, baseline body mass index (BMI), educational level, self- or proxy-reporting, smoking status, living status, and living arrangement

Table 5.3. Characteristics of study included in the meta-analysis examining the associations between dietary pattern, diet quality, and Parkinson disease

Author (year) (reference)	Study characteristics			Mean/median age (year); sex (% female)	Dietary assessment		Adjusted covariates	Outcome assessment	Results	Study quality [1]
	Cohort (country)	Design (follow-up periods, year)	Sample size		Diet assessment method	Evaluation of dietary pattern/diet quality				
Gao X et al. (2007) (19)	The Health Professional Follow-Up Study and the Nurses' Health Study (USA)	Prospective (mean: 16 years)	131,368	52.1; 62.1%	Validated semiquantitative food frequency questionnaire	Dietary pattern scores generated by principal component analysis, the alternate Heathy Eating Index, and alternate Mediterranean diet score	Age, smoking status, BMI, use of nonsteroidal anti-inflammatory drugs, and intakes of total energy, caffeine, and alcohol	Biennial self-reported questionnaires; confirmed with medical record review by neurologist	*Prudent dietary pattern*: Participants with higher score had lower risk of PD (*p*-trend=0.04) *Western dietary pattern*: No significant association between dietary pattern score and risk of PD was observed (adjusted RR=1.29; 95% CI: 0.71-2.34) *Alternate*	8

Health Eating Index: Participants in the highest score quintile had lower risk of PD (adjusted RR=0.70; 95% CI: 0.51-0.94; *p*-trend=0.01)
Alternate Mediterranean Diet Score: No significant association between diet quality and risk of PD was observed (adjusted RR=0.75; 95% CI: 0.57-1.00)

Alcalay RN et al. (2012) (17)	The Center for Parkinson 's Disease (CPD) and Washingt on Heights-Inwood Columbia Aging Project (WHICA P) (USA)	Case-control	455	70; 46.4%	Willett semiquantitati ve food frequency questionnaire	The Mediterrane an diet score	Age, education, and race	Evaluated and diagnosed by movement disorders specialists	Compared with participants in the low Mediterrane an score group, those in the high Mediterrane an score group had lower odds of having PD (adjusted OR=0.48, 95% CI: 0.28-0.82)	5
Okubo H et al. (2012) (18)	Multi-centre hospital (Japan)	Case-control	617	67.4; 62.1%	Validated, self-administered diet history questionnaire	Dietary pattern scores generated by factor analysis	Gender, age, region, pack-years of smoking, education, and BMI	The UK PD Society Brain Bank clinical diagnostic criteria; diagnosed by the collaboratin g neurologists	Participants in the highest quartile of healthy dietary pattern score had lower odds of having PD compared with those in the lowest quartile (adjusted OR=0.54; 95% CI: 0.32-0.92)	5

Sa¨a¨ksja¨rvi K et al. (2013) (15)	The Finnish Mobile Clinic Health Examination Survey (FMC) (Finland)	Prospective (mean: 41 years)	4,524	53.3; 47.2%	Dietary history interview conducted by trained interviewers	Modified alternate Healthy Eating Index	Age, sex, marital status, community density, geographical area, smoking, BMI, leisure-time physical activity, energy, hypertension, serum total cholesterol, diabetes, and parity in women	Identified through linkage with the nationwide Drug Imbursement Register of the Social Insurance Institution and re-evaluated by study neurologist based on National Institute of Neurological Disorders and Stroke diagnostic criteria	No significant association between diet quality score and risk of developing PD was observed (*p*-trend>0.05 for both males and females)	9

[1] Assessed using Newcastle-Ottawa Scale star

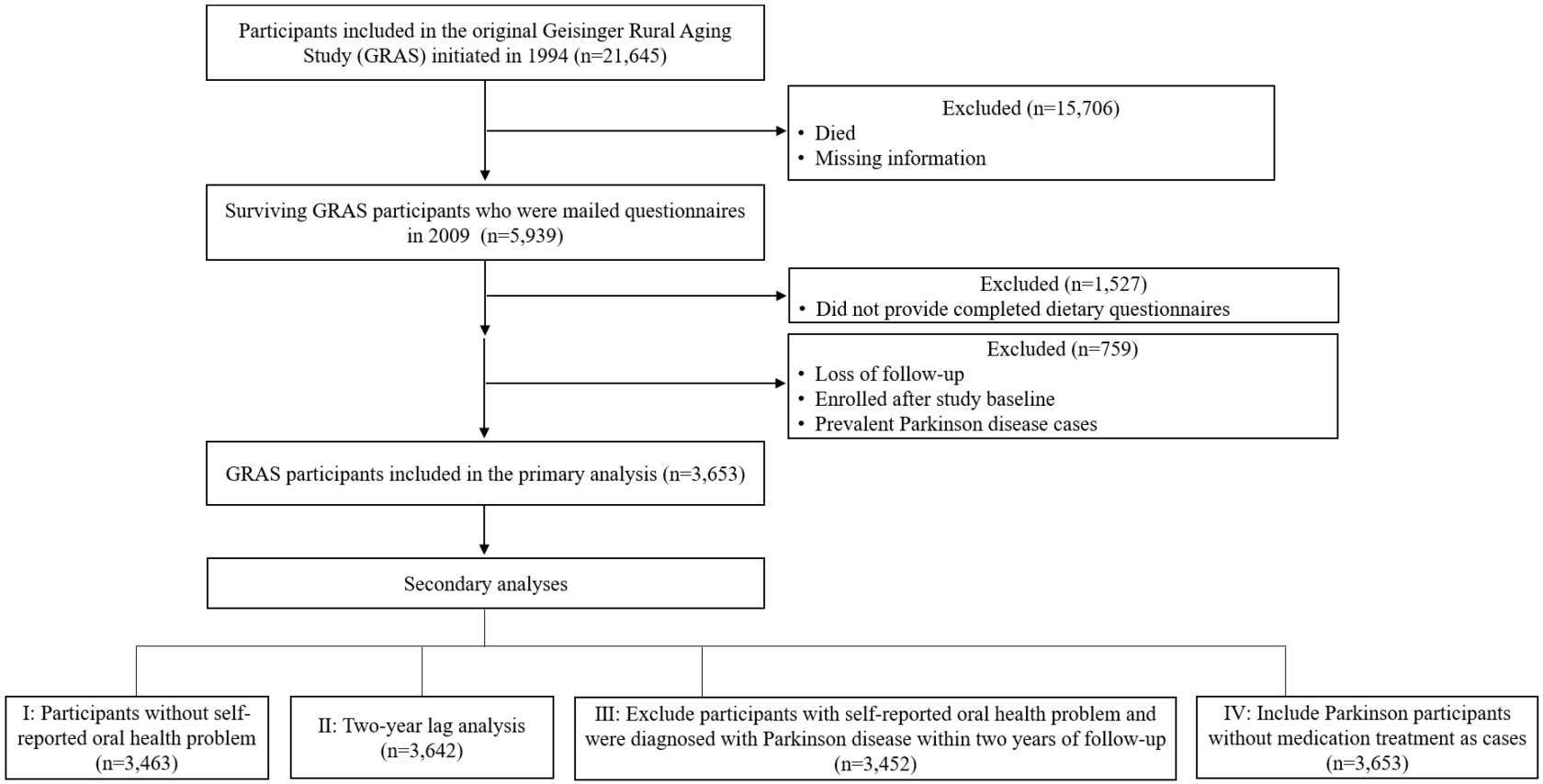

Figure 5.1. Flow chart of Geisinger Rural Aging Study (GRAS) participants. A total of 21,645 older adults were enrolled in GRAS longitudinal cohort starting from 1994. Mailed surveys were sent to 5,939 surviving GRAS participants in 2009. Among participants who received surveys, 3,653 of them returned completed survey and did not have prevalent Parkinson disease at baseline and were therefore followed through September 2019.

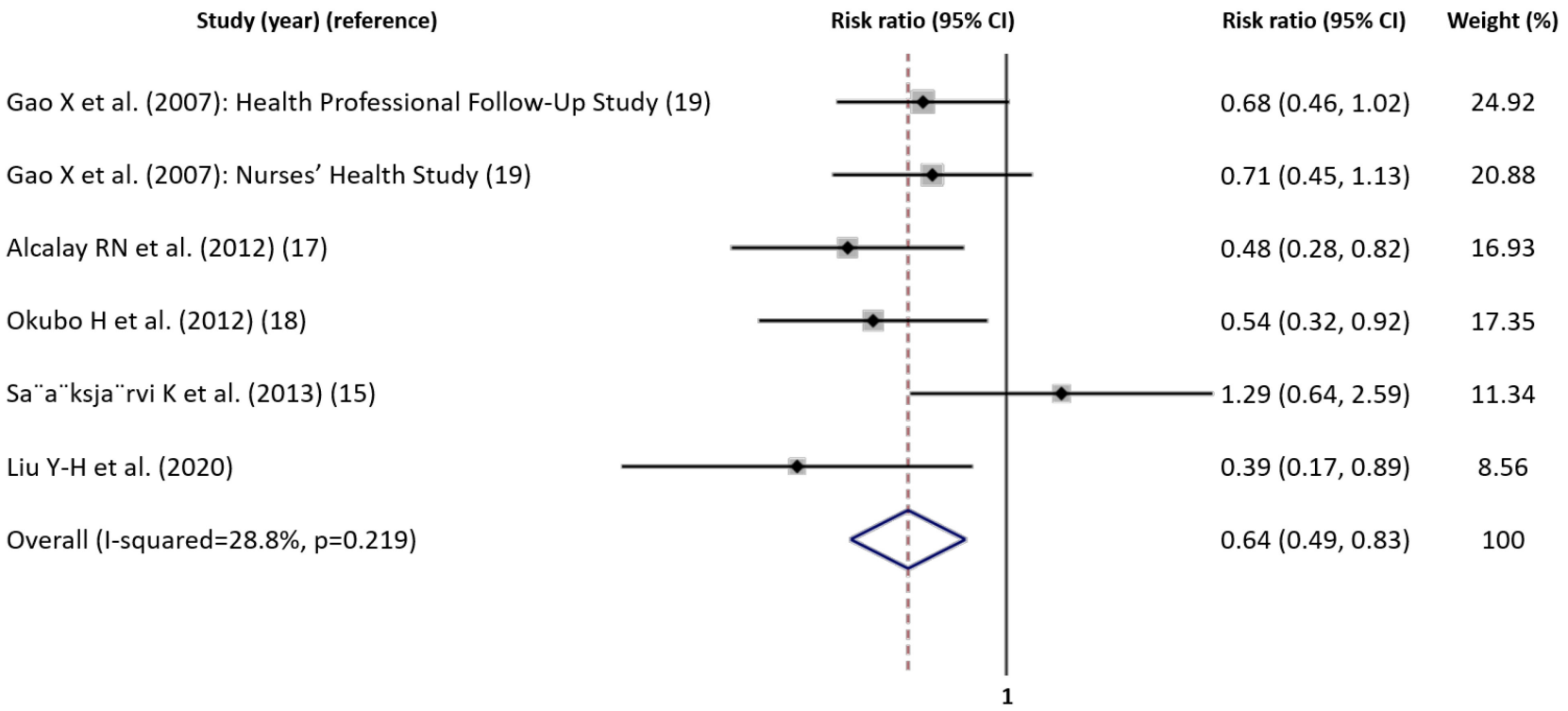

Figure 5.2. The association between diet quality[1] and risk of Parkinson disease (risk ratio for the highest versus the lowest diet quality or dietary pattern). (95% CI: confidence interval)

[1] Studies using diet quality: Gao X et al. (2007), Alcalay RN et al. (2012), Sa¨a¨ksja¨rvi K et al. (2013), and Liu Y-H et al. (2020); study using dietary pattern: Okubo H et al. (2012)

Supplementary materials

Table 5.4. (Supplementary Table 1) Search strategies used in PubMed, Web of Science, and Cumulative Index for Nursing and Allied Health (CINAHL) electronic databases

Database	Search terms	Literatures identified on 11/06/2019
PubMed	("healthy diet"[Mesh] OR "healthy diet"[TW] OR "Healthy diets"[TW] OR "Healthy Eating"[TW] OR "Healthy Eating Index"[TW] OR "Healthy Eating Indices"[TW] OR "diet quality"[TW] OR "dietary quality"[TW] OR "diet pattern"[TW] OR "diet patterns"[TW] OR "dietary pattern"[TW] OR "dietary patterns"[TW] OR "dietary habit"[TW] OR "dietary habits"[TW] OR "diet habit"[TW] OR "diet habits"[TW] OR "eating pattern"[TW] OR "eating patterns"[TW] OR "food pattern"[TW] OR "food patterns"[TW] OR "diet"[Mesh]) AND ("Parkinson Disease"[Mesh] OR "Parkinson Disease"[TW] OR "Parkinson's Disease"[TW] OR "Parkinson"[TW] OR "Parkinson's"[TW]) AND ("Cohort Studies"[Mesh] OR "Cohort"[TW] OR "Observational Studies as Topic"[Mesh] OR "observational"[TW] OR "Prospective Studies"[Mesh] OR "prospective"[TW] OR "Longitudinal Studies"[Mesh] OR "Longitudinal Study"[TW] OR "Longitudinal Survey"[TW] OR "Longitudinal Surveys"[TW] OR "longitudinal"[TW] OR "Retrospective Studies"[Mesh] OR "retrospective"[TW] OR "Case-Control Studies"[Mesh] OR "Case-Control Studies"[TW] OR "Case-Control Study"[TW] OR "case control study"[TW] OR "case control studies"[TW])	100

Web of Science	TS=("healthy diet" OR "Healthy diets") OR TS=("Healthy Eating" OR "Healthy Eating Index" OR "Healthy Eating Indices") OR TS=("diet quality" OR "dietary quality") OR TS=("diet pattern" OR "diet patterns" OR "dietary pattern" OR "dietary patterns") OR TS=("dietary habit" OR "dietary habits" OR "diet habit" OR "diet habits") OR TS=("eating pattern" OR "eating patterns" OR "food pattern" OR "food patterns") AND TS=("Parkinson Disease" OR "Parkinson's Disease" OR "Parkinson" OR "Parkinson's") AND TS=("Cohort Studies" OR "Cohort" OR "observational" OR "Prospective Studies" OR "prospective" OR "Retrospective Studies" OR "retrospective" OR "Longitudinal Studies" OR "longitudinal" OR "longitudinal Survey" OR "Longitudinal Surveys" OR "Case-Control Studies" OR "Case-Control Study" OR "case control study" OR "case control studies")	27

CINAHL	(TX "healthy diet" OR TX "healthy diets") OR (TX "Healthy Eating" OR TX "Healthy Eating Index") OR TX "Healthy Eating Indices" OR (TX "diet quality" OR TX "dietary quality") OR (TX "diet pattern" OR TX "diet patterns") OR (TX "dietary pattern" OR TX "dietary patterns") OR (TX "dietary habit" OR TX "dietary habits") OR (TX "diet habit" OR TX "diet habits") OR (TX "eating pattern" OR TX "eating patterns") OR (TX "food pattern" OR TX "food patterns") OR (TX "diet" OR MH "diet") AND (MH "Parkinson Disease" OR TX "Parkinson Disease" OR TX "Parkinson's Disease" OR TX "Parkinson" OR TX "Parkinson's") AND (TX "cohort studies" OR TX "cohort" OR TX "observational") OR (MH "Prospective Studies" OR TX "prospective" OR TX "Longitudinal Studies" OR TX "longitudinal" OR TX "longitudinal Survey" OR TX "Longitudinal Surveys") OR (MH "Retrospective Design" OR TX "retrospective") OR (MH "Case Control Studies" OR TX "Case Control Studies" OR TX "Case Control Study" OR TX "Case-Control Studies" OR TX "Case-Control Study")	96

Table 5.5. (Supplementary Table 2) Study inclusion and exclusion criteria

Component	Inclusion criteria	Exclusion criteria
Date range	Up to November 6, 2019	
Language	English	Other languages
Study design	Prospective cohort, retrospective cohort, case-control	Cross-sectional
Population	Adults or older adults	-
Exposure	Studies were selected if assessing participants overall dietary pattern or diet quality using a priori or a posteriori approach (i.e. the Mediterranean diet score)	Single nutrient, selective multiple nutrients (i.e. omega-3 consumption)
Outcome	Clinically diagnosed Parkinson disease	Subjective assessment

Table 5.6. (Supplementary Table 3) Association between individual Dietary Screening Tool (DST) component score and risk of Parkinson disease in Geisinger Rural Aging Study (GRAS) (n=3,653)

DST component	Hazard Ratio (95% CI) [1, 2]	*p*-value
1) How often do you usually eat fruit as a snack?	0.81 (0.67, 0.98)	0.03
2) How often do you usually eat whole grain breads?	0.94 (0.82, 1.07)	0.36
3) How often do you usually eat whole grain cereals?	0.84 (0.74, 0.96)	0.01
4) How often do you usually eat candy or chocolate?	0.89 (0.71, 1.12)	0.32
5) How often do you eat crackers, pretzels, chips, or popcorn?	0.93 (0.74, 1.16)	0.50
6) How often do you eat cakes or pies?	0.77 (0.60, 0.99)	0.04
7) How often do you eat cookies?	0.97 (0.76, 1.23)	0.78
8) How often do you eat ice cream?	1.10 (0.85, 1.42)	0.48
9) How often do you eat cold cuts, hot dogs, lunchmeats or deli meats?	1.03 (0.86, 1.23)	0.75
10) How often do you eat bacon or sausage?	1.11 (0.82, 1.49)	0.51
11) How often do you eat carrots, sweet potatoes, broccoli, or spinach?	0.93 (0.83, 1.05)	0.23

12) How often do you eat fruit (not including juice)? Please include fresh, canned or frozen fruit	0.88 (0.75, 1.04)	0.14
13) How often do you eat hot or cold breakfast cereal?	0.82 (0.69, 0.96)	0.02
14) How often do you drink some kind of juice at breakfast?	0.79 (0.68, 0.91)	0.002
15) How often do you eat chicken or turkey?	0.92 (0.77, 1.09)	0.32
16) How often do you drink a glass of milk?	0.93 (0.78, 1.11)	0.43
17) Do you usually add butter or margarine to foods like bread, rolls, or biscuits?	1.09 (0.50, 2.36)	0.83
18) Do you usually add fat (butter, margarine or oil) to potatoes and other vegetables?	0.57 (0.26, 1.29)	0.18
19) Do you use gravy (when available) at meals?	1.24 (0.64, 2.41)	0.52
20) Do you usually add sugar or honey to sweeten your coffee or tea?	1.13 (0.59, 2.15)	0.72
21) Do you usually drink wine, beer or other alcoholic beverages?	0.97 (0.78, 1.19)	0.74
22) How often do you eat fish or seafood that IS NOT fried?	0.93 (0.77, 1.13)	0.48
23) How many servings of milk, cheese, or yogurt do you usually have each DAY?	1.03 (0.47, 2.25)	0.95

24) How many different vegetable servings do you usually have at your main meal of the day?	0.92 (0.80, 1.06)	0.27
25) Which of the following best describes your nutritional supplement use?	1.03 (0.92, 1.16)	0.58

[1] Adjusted for age, sex, race, baseline body mass index (BMI), educational level, self- or proxy-reporting, smoking status, living status, living arrangement, and oral health status

[2] The association between one point increase in the DST component score and risk of Parkinson disease

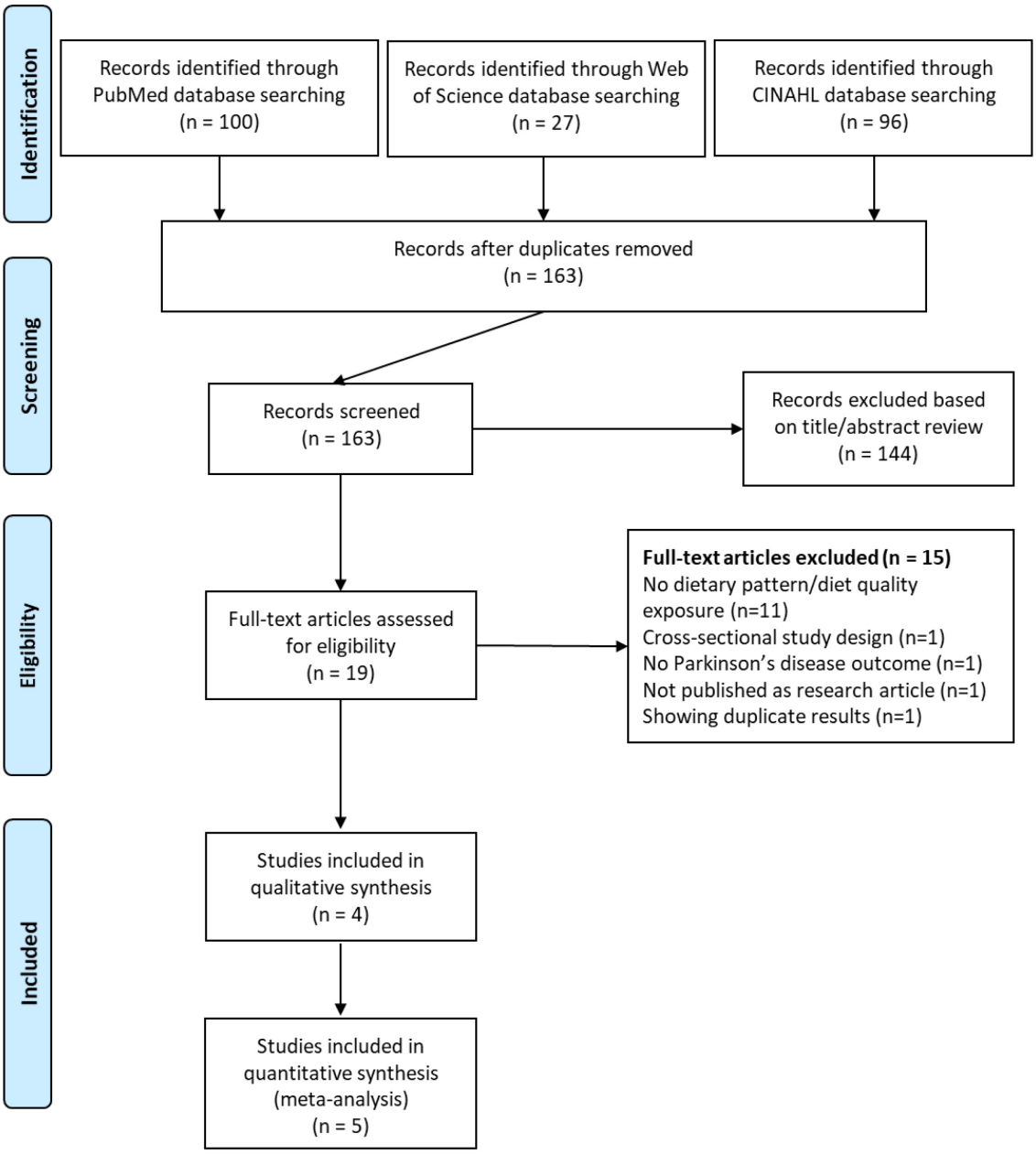

Figure 5.3. (Supplementary Figure 1) Flow diagram of study selection process. A total of 163 studies were identified through three electronic databases. After title/abstract and full-text review, 4 studies met the inclusion criteria and were included in the meta-analysis along with our prospective study. (CINAHL: Cumulative Index for Nursing and Allied Health)

CHAPTER 6

CONCLUSIONS

Summary of research findings and implications

The main purpose of this dissertation research was to validate a diet quality screening tool for application among the oldest old aged ≥80 years and further relate diet quality to risk of mortality and Parkinson disease. Three objectives were included and examined: 1) to perform validation analyses of a dietary screening tool among the oldest old; 2) to prospectively examine the association between diet quality and risk of mortality in the oldest old; 3) to examine the association between diet quality and Parkinson disease in a prospective cohort including older adults and in a meta-analysis.

The DST was developed in prior studies among GRAS participants ≥65 years of age residing in rural Pennsylvania and then validated within a cross-sectional cohort that included 204 older adults aged ≥65 years (1, 2). Having high diet quality, as assessed by the DST, was associated with more favorable biochemical indicators of nutritional status compared with low diet quality (2). However, little is known regarding the validity of the DST in assessing diet quality among the oldest old aged ≥80 years. Objective 1 was thus addressed in chapter 3, aiming to examine whether the DST is a valid measurement of diet quality in a cross-sectional subset of the GRAS cohort including 122 participants aged ≥80 years. We observed that the oldest old who had high diet quality, assessed by the DST, had significantly higher HEI score (adjusted means=79.6 ± 3.68) compared with those having medium (adjusted means=66.3 ± 1.70) and low diet quality (adjusted means=51.2 ± 1.56) after adjusting for age and sex. Adjusting for additional risk factors, including BMI, serum cholesterol, blood glucose, triglyceride, and history of diabetes, coronary artery disease, hypertension, liver disease, obstructive sleep apnea, depression,

and osteoarthritis did not change the observed association. A significant association between the DST score and the HEI score was also observed (adjusted r=0.68; p<0.001). In order to confirm the relative validity of the DST and examine potential bias, a Bland-Altman plot was generated using standardized z-scores of the DST and the HEI. No consistent bias was observed in the Bland-Altman plot, indicating the randomness and agreement between the DST and the HEI. These pieces of evidence suggest the DST to be an effective diet quality screening tool for the oldest old. It may therefore offer the opportunity for prevention and early detection of malnutrition to improve health outcomes and quality of life.

One of the difficulties in examining the relationship between diet quality and health outcomes in the oldest old was the lack of a diet quality screening tool that is validated for use in a population of such advanced age. Once we validated the DST for this application, we were able to further investigate the relationship of diet quality and risk of comorbidities and mortality. Objective 2 was presented in chapter 4, examining the association between diet quality and mortality in 1,990 participants ≥80 years of age among the GRAS cohort. In this study, we observed that high diet quality, assessed by the DST, was associated with lower risk of mortality after 8 years of follow-up (adjusted HR=0.76; 95% CI: 0.59-0.97; p-trend=0.04). This observed association was consistent across statistical models adjusting for age, sex, baseline BMI, self- or proxy-reporting, smoking status, living arrangement, self-reported oral health status, baseline Charlson index score of comorbidity, and educational level. In addition, there was no effect modification by potential risk factors observed in our interaction analyses. Our sensitivity

analyses that excluded participants with self-reported oral health problem(s) or higher disease burden also supported this inverse association. Moreover, we observed a potential linear association between higher diet quality and lower risk of mortality in the spline model. Our study builds upon and agrees with a prior GRAS study investigating diet quality and mortality in older adults (3). Similar associations were also reported by McNaughton SA et al (4) and Reedy J et al (5). Findings from our prospective study emphasized the potential role of lifestyle factors, particularly diet quality, on risk of mortality among the oldest old and may help provide guidance on dietary recommendations for healthy aging.

In chapter 5 we further related diet quality to Parkinson disease using the DST. Objective 3 was addressed by examining the association between diet quality and risk of Parkinson disease among 3,653 older adults ≥65 years of age within the GRAS cohort in a prospective study and then further conducting a meta-analysis. Participants with high diet quality had lower risk of Parkinson disease compared with those with low diet quality during a mean of 6.94 years of follow-up after adjusting for potential confounders, including age, sex, race, baseline BMI, educational level, self- or proxy-reporting, smoking status, living status, living arrangement, and oral health status (adjusted HR=0.39; 95% CI: 0.17-0.89; *p*-trend=0.02), suggesting the observed association to be independent of potential risk factors. Furthermore, we observed similar trends among sensitivity analyses excluding participants with self-reported oral health problem(s) and those diagnosed with Parkinson disease within two years of follow-up. We did not find significant interactions between diet quality and potential risk factors.

Next we conducted a meta-analysis that pooled results from our prospective study with 4 related published studies, thereby including a combined 140,617 individuals. These findings suggested that adherence to a high-quality diet was associated with lower odds of having Parkinson disease. In contrast with our research, a prospective study conducted in a Finnish cohort with a mean follow-up of 41 years observed no association between diet quality and incidence of Parkinson disease (6). The lack of association may be explained by the possibility that the food components included in diet quality index used in the Finnish study were not related to risk of Parkinson disease. However, our findings in older persons are in line with results from a prospective study including 131,368 participants in the United States with mean age ranging from 48.8 to 56.5 years old at baseline that observed that adherence to a healthy dietary pattern or a high-quality diet, as assessed by the AHEI, was associated with lower risk of incident Parkinson disease (7). Findings from our prospective study and meta-analysis suggest that there may be potential to modify diet as a modifiable lifestyle factor in preventing or slowing the pathogenesis of Parkinson disease. However, more observational studies are warranted to examine the generalizability of our findings and to better guide dietary recommendations for Parkinson disease prevention.

Strengths and limitations

To the best of our knowledge, the DST is the first diet quality screening tool that has been validated for the assessment of overall diet quality among the oldest old. We validated the DST against the HEI, which is a measure of the adherence to the Dietary Guidelines for Americans. We also found that low diet quality as measured by the HEI is associated with risk of mortality and comorbidities (8-11). Of note, previous validation studies have also found the DST to be a valid measurement of diet quality among adults aged ≥65 years in a subset of the GRAS cohort (2) and in a middle-aged cohort in Appalachia (12). The DST may prove to be a practical tool in detecting diet quality in other populations, but will warrant further testing and possible modification for such applications.

Our mortality analysis is also the first study to examine the relationship between diet quality and risk of mortality restricting the population sample to only those ≥80 years of age. We observed an inverse association between overall diet quality and mortality risk which was not confounded or modified by potential risk factors, including age, sex, obesity, and disease burden. Our diet quality and Parkinson disease analysis is also the first prospective study with participants ≥65 years of age and the first meta-analysis extracting and summarizing evidence on this topic. Findings suggest that adoption of a high-quality diet may lower risk of Parkinson disease and promote healthy aging.

Although we conducted a validation analysis to demonstrate the validity of the DST for use in the oldest old and further related overall diet quality to risk of mortality

and Parkinson disease, there are some limitations that must be acknowledged. First, we were unable to estimate participants' energy intake using the DST, because of the scoring design of the instrument and the limited food components included. We did however observe significant correlations between the DST and the HEI-2015, which was calculated based upon three 24-hour dietary recalls. It is also important to recognize that the DST was developed and validated in the GRAS cohort of older adults living in rural Pennsylvania with limited diversity in race and lifestyle habits. Because the DST was developed using population specific food- and behavior-related questions, items included in this dietary screening tool may not be applicable to other populations. The validity of using the DST among cohorts with different ethnic backgrounds, regions, and characteristics requires further investigation. The relatively high non-completion rate (30%) of the 24-hour dietary recalls that were undertaken for our validation study suggest that selection bias may be an additional limitation in our validation testing.

Reverse causality is a potential limitation for our mortality and Parkinson studies (13). An older population that had appreciable underlying disease burden may have already had changes in dietary habits prior to being diagnosed. To address this concern, we adjusted for baseline disease burden in the statistical model and further conducted lag analyses by excluding participants who died within 2 and 4 years of follow-up in our mortality study. Similar associations between diet quality and risk of mortality were observed. However, it is possible that individuals with Parkinson disease may have been in a preclinical phase without symptoms when their diet quality was assessed due to the long preclinical period that is characterized in the development of Parkinson disease (14).

Although we observed a similar trend between diet quality and risk of Parkinson disease in the 2-year lag analysis, the concern of reverse causality cannot be fully excluded due to the long prodromal period of Parkinson symptoms before the clinical onset.

Another notable limitation would be the lack of repeated diet quality assessments during follow-up in the GRAS cohort. In our studies, overall diet quality was only assessed at baseline using the DST which may underestimate the impact of changes in diet quality over time on disease outcomes. Although some studies have observed diet quality and dietary pattern remained stable among peri-retirement adults (15) and older adults (16), we still cannot exclude the possibility of changes in diet quality especially with the oldest old participants who were more susceptible to age-related functional decline and physiological changes.

While our study suggests baseline diet quality was inversely associated with risk of mortality after 8 years of follow-up, it remains unclear whether participants with low baseline diet quality would have lower risk of mortality by improving diet quality during follow-up. However, Sotos-Prieto M et al. reported that improved diet quality during 12 years of follow-up was significantly associated with lower risk of death (17). In this longitudinal study conducted among 47,994 women in the Nurses' Health Study and 25,745 men in the Health Professionals Follow-up Study, the AHEI, the alternate Mediterranean diet score, and the DASH score were used to assess changes in diet quality (17). Compared with individuals with stable diet quality (defined as 0-3% increases), those with the largest improvement in diet quality (defined as 13-33% increases) had lower risk of all-cause mortality during 12 years of follow-up, as assessed by the AHEI

(pooled HR=0.91; 95% CI: 0.85-0.97), the alternate Mediterranean diet score (pooled HR=0.84; 95% CI: 0.78-0.91), and the DASH score (pooled HR=0.89; 95% CI: 0.84-0.95) (17). Although this study was conducted among adults in their early 60s at baseline, it provides evidence on potential health benefits from improvement of diet quality over time.

Smoking status tended to be under-reported in the GRAS cohort with 2.6% and 3.4% of participants identified themselves as a past or current smoker in the mortality study and Parkinson study, respectively. This under-estimated smoking behavior may result in potential residual confounding as smoking was previously found to be associated with low diet quality (18).

One potential limitation in our meta-analysis is that the methods of diet quality and dietary pattern assessment varied across the included studies, which may hinder the interpretation of findings and comparison among studies. However, many similarities are recognized among the known high-quality diets or healthy dietary patterns, such as reduced consumption of saturated fats and red meat as well as high intake of fruits, vegetables, and whole grains. Another limitation would be the small number of studies included in our meta-analysis which led to restriction in conducting subgroup analyses to address study heterogeneity. Although we conducted a comprehensive systematic literature search in three electronic databases, only 4 studies examining the association between overall diet quality or dietary pattern and risk of Parkinson disease met our inclusion criteria.

Directions for future research

In order to better understand the relationship between overall diet quality, mortality, Parkinson disease, and other chronic disease outcomes, there are several directions that future research may examine and address:

1. Findings from the GRAS cohort suggest the DST to be a valid measure of overall diet quality among older adults and the oldest old residing in rural Pennsylvania. However, the DST should be tested in diverse older populations to examine its broader validity and to further relate diet quality to risk of mortality and comorbidities.
2. As suggested by Harmon BE et al. (19), ethnicity and sex may affect findings generated from various diet quality indices. Comparing different diet quality indices in a same cohort may help address culture- or sex-specific dietary characteristics. In addition, further exploring the relationship using both *a priori* and *a posteriori* diet assessments would also be valuable.
3. Although diet quality has been considered relatively constant overtime during older adulthood, future studies with multiple assessments of diet quality would assist in addressing whether change(s) in diet quality over time may be more strongly associated with risk of comorbidities. The magnitude of change(s) in diet quality over time would be of particular interest.
4. More large-scale prospective studies with longer duration of follow-up are needed to better understand the long-term effects of diet quality on comorbidities and related mortality.

5. The majority of studies have focused on diet quality and disease and mortality outcomes among adults in general or adults ≥65 years of age. Therefore, additional prospective studies focused on the oldest old ≥80 years of age are warranted to examine the generalizability of our findings to other populations of advanced age.
6. Performing further systematic reviews and meta-analyses of prospective studies specifically conducted in older adults to extract and summarize up-to-date findings may assist in providing guidance for evidence-based dietary recommendations for older populations.

In conclusion, this dissertation presented findings that demonstrated the validity of the DST as a measure of diet quality among the oldest old. Diet quality was also related to risk of mortality and risk of Parkinson disease. Our study results suggest that diet quality, assessed by the DST, was significantly associated with all-cause mortality in the oldest old and incident Parkinson disease in older adults independent of known risk factors. Due to the methodological limitations mentioned above, future prospective studies are required to confirm the observed relationships between diet quality and comorbidity and mortality outcomes.

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VITA
Yi-Hsuan Liu

Education

Dual-title Ph.D. in Nutritional Sciences and Clinical and Translational Science 2016-2020
The Pennsylvania State University, University Park, PA
M.S. in Human Nutrition 2012-2015
The Ohio State University, Columbus, OH
B.S. in Nutrition and Health Sciences 2008-2012
Taipei Medical University, Taipei, Taiwan

Selected publications

Liu Y-H, Jensen GL, Na M, Mitchell DC, Wood C, Still CD, Gao X. Diet quality and risk of Parkinson disease: a prospective study and a meta-analysis. 2020 (under review)

Liu Y-H, Gao X, Na M, Kris-Etherton PM, Mitchell DC, Jensen GL. Dietary pattern, diet quality, and dementia: a meta-analysis and a systematic review of prospective cohort studies. 2020 (under review)

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Honors and awards

Finalist, Clinical Emerging Leaders Award, American Society for Nutrition 2019
Finalist, Emerging Leader in Nutrition Science Poster Competition 2019
American Society for Nutrition
Penn State NIH-funded CTSI TL1 Career Development Fellowship 2018
Finalist, Emerging Leader in Nutrition Science Poster Competition 2018
American Society for Nutrition
North America Chinese Society for Nutrition/American Society for Nutrition joint travel award 2017
Finalist, Emerging Leader in Nutrition Science Poster Competition 2017
American Society for Nutrition
Graham Endowed Fellowship, The Pennsylvania State University Graduate School 2016