HEALTH INDICATORS THAT INFLUENCE THE RISK OF ALL-CAUSE
MORTALITY AND FUNCTIONAL DECLINE IN OLDER PERSONS

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by

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ABSTRACT

The percentage of persons aged 65 years or older in the United States is growing rapidly, from 13.7% in 2012 to a projected 20.9% in 2050. The prevalence of overweight or obesity is increasing across all age groups, including older adults. Nearly 71% of United States adults aged 60 years or older are either overweight or obese (body mass index (BMI) 25 kg/m² or above); approximately 31% of them are obese (BMI 30 kg/m² or above). Although elevated BMI is a strong risk factor for adverse health outcomes among younger and middle-aged adults, studies have suggested that overweight or mild obesity may confer no additional or even lower all-cause mortality risk among older individuals. However, the explanation for this “obesity paradox” is still unclear and this phenomenon has sparked great controversy in the medical and nutrition communities over the years.

The objective for our first study was to investigate the association between baseline BMI and all-cause mortality in a well characterized cohort of older persons, controlling for age, sex, smoking, alcohol, laboratory values, medications, and comorbidity status. To address crucial methodological issues, such as reverse causation and residual confounding, we restricted our secondary analyses to never-smokers with no major chronic diseases, excluded early deaths, and used a propensity score approach. This was a prospective cohort study of 4,565 Geisinger Rural Aging Study (GRAS) participants with a baseline age of 74±4.7 (mean±SD) and a BMI of 29.5±5.3 over a mean of 10.9±3.8 years of follow-up. There was a U-shaped association between BMI and all-cause mortality when we treated BMI as a continuous variable using a restricted cubic spline approach ($P$-non-linearity<0.001). A similar pattern also was noted when we
categorized participants according to the National Institutes of Health (NIH) BMI guidelines (18.5 to 24.9 desirable, 25.0 to 29.9 overweight, 30.0 to 34.9 class I obesity, and ≥ 35.0 kg/m² classes II/III obesity). After accounting for age, sex, smoking, alcohol, laboratory values, medications, and comorbidity status, underweight (BMI <18.5 kg/m²) individuals had significantly greater adjusted risk of all-cause mortality than participants with a BMI between 18.5 and 24.9 kg/m² (reference range). Participants with overweight (BMI 25.0 to 29.9 kg/m²) or class I obesity (BMI 30.0 to 34.9 kg/m²) had significantly lower adjusted risk of all-cause mortality. Interestingly, this adjusted mortality risk was not significantly higher among those with class II or III obesity (BMI ≥35.0 kg/m²).

Findings remained consistent when using propensity score weights or including only never-smokers with 2-and 5-year lag analysis or with no identified chronic diseases.

The objective for the second study was to examine the joint effects of BMI class and metabolic health in relation to all-cause mortality in a well-characterized cohort of older persons. To reduce the impact of reverse causation and residual confounding on the potential relation between obesity/metabolic health and mortality, we conducted multiple sensitivity analyses using propensity score weights and also by excluding smokers with no identified chronic disease burden or those who had early deaths. This prospective study was based on the same cohort as the first study, except we further eliminated those with a BMI <18.5 kg/m² (n=14) (i.e., 4,551 participants remained for the final analysis). Study participants, with a baseline age of 74±4.7 (mean±SD), were categorized according to the NIH BMI guidelines and the presence or absence of a metabolically healthy phenotype (i.e., 0 or 1 risk factors based on a modified Adult Treatment Panel III). A metabolically unhealthy phenotype was defined as having 2 or more risk factors. There
were 2,294 deaths over a mean 10.9±3.8 years of follow-up. Relative to metabolically healthy desirable weight, metabolically healthy overweight or class I obesity was not associated with a greater mortality risk (HR: 0.90; 95 CI%: 0.73, 1.13 and HR: 0.58; 95 CI%: 0.42, 0.80, respectively) \((P\text{-interaction}<0.001)\). Results persisted even when using a propensity score approach or when including only never-smokers with no identified chronic disease burden or with 5-year lag analysis.

The objective for the third study was to use conditional inference tree analysis to construct a risk stratification algorithm for risk of developing functional decline, based on BMI and other potential risk factors (e.g., age, sex, lifestyle factors, and disease burden) among GRAS participants who reported no functional limitations at baseline. This prospective study was based on the same cohort as the first study, except we further excluded 2,614 individuals who either 1) did not complete baseline (i.e., between 1999 and 2003; n=982) or follow-up (i.e., between 2009 and 2011; n=1,371) functional status questionnaire due to death or other reasons or 2) had baseline functional limitation (i.e., indicated having any of the activities of daily living (ADL) or instrumental activities of daily living (IADL); n=261). This resulted in 1,951 individuals for the final analysis (i.e., 4,565-2,614=1,951). For comparison, we also analyzed the data using multivariate stepwise logistic regression. A total of 221 individuals developed functional limitation (i.e., reported having difficulty with any ADLs or IADLs) over a mean 9.2±1.7 years of follow-up. Both analytic approaches identified higher BMI, age, and comorbidity as significant risk factors for functional decline. Conditional inference tree analysis further stratified individuals into four risk groups based on these three risk factors. Compared to the low risk group, all other risk groups had significantly greater risk of developing
functional limitation. The odds ratio comparing the two extreme categories was 9.09 (95% CI: 4.68, 17.6).

The objective for the fourth study was to perform a meta-analysis of observational cohort studies to examine current literature on the association between weight change (weight loss, weight gain, and weight fluctuation) and all-cause mortality among older adults aged 60 years or older. We used three databases – PubMed (MEDLINE), Web of Science, and Cochrane Library – to identify prospective studies published in English from inception to November 2014. This meta-analysis included 17 prospective studies that met the inclusion criteria. Overall, we observed a higher all-cause mortality risk with weight change: weight loss (pooled relative risk (RR): 1.67; 95% CI: 1.51, 1.85; $P<0.001$ for heterogeneity), weight gain (pooled RR: 1.21; 95% CI: 1.09, 1.33; $P=0.03$ for heterogeneity), and weight fluctuation (pooled RR: 1.53; 95% CI: 1.36, 1.72; $P=0.43$ for heterogeneity). Results from sensitivity analyses with stricter criteria showed similar patterns. None of the study characteristics had statistically significant effects on the pooled RR, except for study quality on weight loss.

In conclusion, our results support the obesity paradox among older persons. We observed a U-shaped association between BMI and all-cause mortality with lower risk in individuals with overweight or mild obesity (class I obesity), compared to those with a BMI between 18.5 and 24.9 kg/m². Our findings did not support the suggestion that residual confounding by smoking or reverse causation due to early deaths, disease burden, and smoking could explain this phenomenon. Our results do however suggest that the obesity paradox may be partially explained by the inclusion of metabolically healthy overweight and obese older persons, who do not have elevated mortality risk, in
population studies of BMI and mortality. However, it is important to highlight that higher BMI was consistently identified as a significant risk factor for functional decline using both traditional regression and data mining approaches in our study. Therefore, it is imperative to consider the impact of overweight or obesity on other health and functional outcomes when considering any possible mortality benefits. Lastly, while our meta-analysis showed that weight change is associated with higher mortality risk among community-dwelling adults aged 60 years or older, more studies are warranted to provide the specificity needed to develop meaningful public health and clinical guidelines.
TABLE OF CONTENTS

List of Tables .............................................................................................................................................. xi
List of Figures ................................................................................................................................................ xiii
List of Abbreviations ................................................................................................................................... xiv
Acknowledgements .......................................................................................................................................... xv

CHAPTER 1: INTRODUCTION......................................................................................................................... 1

  Background .................................................................................................................................................. 2
  Objectives ................................................................................................................................................... 3
  Dissertation content and format .................................................................................................................. 5
  References ................................................................................................................................................... 7

CHAPTER 2: REVIEW OF THE LITERATURE.................................................................................................... 9

  Introduction ................................................................................................................................................ 10
  Body mass index and all-cause mortality ..................................................................................................... 11
  Impact of body mass index and metabolic health status on all-cause mortality ......................................... 16
  Body mass index and functional decline ..................................................................................................... 18
  Weight change and all-cause mortality ......................................................................................................... 21
  References ................................................................................................................................................ 24

CHAPTER 3: BODY MASS INDEX AND ALL-CAUSE MORTALITY AMONG OLDER ADULTS............................... 32

  Abstract .................................................................................................................................................... 33
  Introduction ................................................................................................................................................ 34
  Methods ..................................................................................................................................................... 36
    Study setting, design, and subjects .............................................................................................................. 36
    Weight, height, and BMI ............................................................................................................................. 37
    Assessment of other covariates ................................................................................................................... 38
    Statistical analyses ................................................................................................................................... 39
  Results ....................................................................................................................................................... 41
    Baseline characteristics ............................................................................................................................. 41
    Association between BMI and all-cause mortality ....................................................................................... 41
    Subgroup analyses .................................................................................................................................... 42
    Sensitivity analyses ................................................................................................................................... 42
  Discussion .................................................................................................................................................. 43
  Conclusions ............................................................................................................................................... 46
  References ................................................................................................................................................. 47
Quality assessment ................................................................. 126
Statistical analysis .................................................................. 126
Results ..................................................................................... 137
Study selection ......................................................................... 137
Study characteristics ................................................................. 137
Weight loss and all-cause mortality ........................................... 137
Weight gain and all-cause mortality ........................................... 141
Weight fluctuation and all-cause mortality ................................. 141
Discussion ................................................................................. 141
Conclusions .............................................................................. 144
Take away points ....................................................................... 144
References ................................................................................ 145

CHAPTER 7: CONCLUSIONS ................................................................. 149

Summary of research findings and implications ......................... 150
Limitations ................................................................................ 157
Directions for future research .................................................... 160
References ................................................................................ 163
LIST OF TABLES

Table 3.1  Baseline Characteristics by Body Mass Index Category (n=4,565)\(^a\) ....51
Table 3.2  All-Cause Mortality in Relation to Body Mass Index (n=4,565)\(^a\) ........53
Table 3.3  All-Cause Mortality in Relation to Body Mass Index: Subgroup Analyses (n=4,565)\(^a\) ...........................................................................54
Table 4.1  Baseline Characteristics of the Study Population, by Body Mass Index Class (n=4,551)\(^a\) ........................................................................................................77
Table 4.2  All-cause Mortality in Relation to Body Mass Index and Metabolic Status (n=4,551)........................................................................................................79
Table 4.3  Subgroup Analyses: All-cause Mortality in Relation to Body Mass Index and Metabolic Status .................................................................80
Table 4.4  All-cause Mortality in Relation to Body Mass Index and Individual Metabolic Components (n=4,551)........................................................................87
Table 4.5  All-cause Mortality in Relation to Body Mass Index and Metabolic Status - Propensity Score Weights (n=4,551)................................................88
Table 4.6  All-cause Mortality in Relation to Body Mass Index and Metabolic Status – Excluding Those on Cholesterol Lowering Medicine (n=2,011) ........................................................................................................89
Table 4.7  All-cause Mortality in Relation to Body Mass Index and Metabolic Status – Excluding Those without Diabetes Diagnosis but On Diabetics Medications (n=4,550)............................................................................................90
Table 4.8  All-cause Mortality in Relation to Body Mass Index and Metabolic Status – Excluding Those without Hypertension Diagnosis but On Blood Pressure Medications (n=4,369) ........................................................................................................91
Table 5.1  Baseline Characteristics of the Study Population, by Functional Limitation Status (n=1,951)\(^a\) ..........................................................112
Table 5.2  5-Fold Cross-Validation: Area Under Receiver Operating Characteristic Curve (AUC) of Conditional Inference Tree Analysis and Logistic Regression Model ..........................................................117
Table 5.3  5-Fold Cross-Validation: Significant Predictors Identified by Conditional Inference Tree Analysis ................................................................118
Table 5.4 Propensity Score Models: Significant Predictors Identified by Conditional Inference Tree Analysis .................................................................119

Table 5.5 Propensity Score Models: Baseline Characteristics of the Lowest and Highest Risk Stratification Groups .................................................................120
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Flow Chart of Geisinger Rural Aging Study (GRAS) Study Participants</td>
<td>6</td>
</tr>
<tr>
<td>3.1</td>
<td>Flow Chart of Geisinger Rural Aging Study (GRAS) Study Participants</td>
<td>56</td>
</tr>
<tr>
<td>3.2</td>
<td>All-Cause Mortality in Relation to Body Mass Index: Restricted Cubic Spline</td>
<td>57</td>
</tr>
<tr>
<td>4.1</td>
<td>Distribution of Metabolic Risk Factors and Metabolic Health Status by Body Mass Index</td>
<td>82</td>
</tr>
<tr>
<td>4.2</td>
<td>All-cause Mortality in Relation to Body Mass Index and Metabolic Status</td>
<td>83</td>
</tr>
<tr>
<td>5.1</td>
<td>Flow Chart of Study Geisinger Rural Aging Study (GRAS) Participants</td>
<td>114</td>
</tr>
<tr>
<td>5.2</td>
<td>Predictors of Developing Any Functional Limitation and Risk Stratification (n=1,951)</td>
<td>115</td>
</tr>
<tr>
<td>5.3</td>
<td>Odds Ratios of Developing Any Functional Limitation Between Risk Groups Identified by Conditional Inference Tree Analysis (n=1,951)</td>
<td>116</td>
</tr>
</tbody>
</table>
LIST OF ABBREVIATIONS

95% CI  95% confidence interval
ADL  activities of daily living
AIC  Akaike Information Criterion
AUC  area under receiver operating characteristic curve
BMI  body mass index
DBP  diastolic blood pressure
EMR  electronic medical records
GRAS  Geisinger Rural Aging Study
HDL  high-density lipoprotein cholesterol
HR  hazard ratio
IADL  instrumental activities of daily living
ICD-9  International Classification of Diseases-9
IRB  Institutional Review Board
kg  kilograms
LDL  low density lipoprotein cholesterol
MEDLINE  Medical Literature Analysis and Retrieval System Online
mg/dL  milligrams per deciliter
mm Hg  millimeter of mercury
mmol/L  millimoles per liter
MOOSE  Meta-Analysis of Observational Studies in Epidemiology
NCEP ATP III  National Cholesterol Education Program Adult Treatment Panel III
NHANES  National Health and Nutrition Examination Survey
NIH  National Institutes of Health
NOS  Newcastle-Ottawa Scale
OR  odds ratio
RR  relative risk
SAS  Statistical Analysis System
SBP  systolic blood pressure
SE  standard error
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Chapter 1

INTRODUCTION
BACKGROUND

The number of United States adults aged 65 years or older is expected to grow considerably, from 43.1 million in 2012 to an estimated 83.7 million in 2050 (1). The prevalence of overweight or obesity continues to rise and is projected to reach nearly 86% of adults in the United States by the year of 2030 (2). This obesity epidemic exists not only among younger and middle-age adults, but it is also observed among older persons. Approximately 71% of United States adults aged 60 years or older are either overweight or obese (body mass index (BMI) 25 kg/m² or above); about 31% of them are obese (BMI 30 kg/m² or above) (3).

Overweight or obesity is a strong risk factor for adverse health outcomes, such as diabetes, hypertension, lower back pain, cardiovascular diseases, pulmonary dysfunction, osteoarthritis, and sleep apnea, among younger and middle-aged adults. It also confers increased mortality risk (4,5). Yet, studies of older persons have suggested that overweight or mild obesity may confer no additional or even lower all-cause mortality risk (6–11). This “obesity paradox” has been a subject of on-going controversy in the medical and nutrition fields. Some researchers suggest that methodological issues, such as residual confounding by smoking or reverse causation due to early deaths, disease burden, and smoking, could explain the obesity paradox. However, this speculation has not been supported by some studies (8,12). Therefore, the explanation for this phenomenon remains unclear and further investigations are warranted.
OBJECTIVES

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

Objective 1: To examine the association between baseline BMI and all-cause mortality in a well-characterized cohort of older persons.

Objective 2: To investigate the joint effects of BMI class and metabolic health in relation to all-cause mortality in a well-characterized cohort of older persons.

Objective 3: To construct a risk stratification algorithm, using conditional inference tree analysis, for risk of developing functional decline, based on BMI and other potential risk factors (e.g., age, sex, lifestyle factors, and disease burden) among older persons who reported no functional limitations at baseline.

Objective 4: To conduct a meta-analysis of observational cohort studies to examine current literature on the association between weight change (weight loss, weight gain, and weight fluctuation) and all-cause mortality among older adults.

The Geisinger Rural Aging Study (GRAS) cohort was used to examine objectives 1, 2, and 3. All GRAS participants were aged 65 years or older, resided in northeastern and central Pennsylvania, and enrolled in the Medicare-managed health maintenance organization administered through the Geisinger Health System (Danville, PA). For the purpose of our studies, we included those who received primary care at the Geisinger Medical Center (Danville, PA) between January 1, 2001 and December 31, 2004 and were active in the electronic medical record (EMR) Epic Systems (Verona, WI).
A total of 6,903 individuals had complete electronic data (i.e., having at least one outpatient diagnosis and complete basic information: age, sex, weight, and height) during this baseline period. We excluded 1,566 and 772 participants because of missing laboratory or smoking/alcohol data, respectively, leaving 4,565 individuals for the final analysis in objective 1. We used the same cohort to explore objective 2 but we further excluded those with a BMI <18.5 kg/m² (n=14) (i.e., 4,551 participants remained for the final analysis). Objective 3 was based on a smaller subset of the GRAS cohort. Of the 4,565 GRAS participants that were evaluated in objective 1, 3,583 of them completed the baseline functional status questionnaire about activities of daily living (ADL) and instrumental activities of daily living (IADL) (13,14) that was mailed between 1999 and 2003. Due to the prospective nature of the study, we excluded individuals (n=261) who had baseline functional limitation (i.e., who reported having any of the ADLs or IADLs). We mailed the same questionnaire for follow-up between 2009 and 2011. Of the remaining 3,322 participants, 598 did not return the questionnaire and 773 had died, leaving 1,951 individuals for the final analysis for objective 3. A flow chart of GRAS study participants is presented in Figure 1.1.

Except for functional status (i.e., ADLs and IADLs) as described in objective 3, all demographic and health information, such as age, sex, weight and height measurements, clinical laboratory values, disease status, smoking status, alcohol usage, and medications, were extracted from the EMR. Mortality data were identified using both the EMR and the Social Security Death Index data through May 23, 2015.

Objective 4 was not based on the GRAS cohort because the goal of this objective was to perform a meta-analysis of existing observational cohort studies that have
examined the association between weight change and all-cause mortality among older persons.

**DISSERTATION CONTENT AND FORMAT**

This dissertation begins with a review of the literature examining the associations between 1) BMI and all-cause mortality, with particular focus on the obesity paradox; 2) the joint effects of BMI and metabolic health status on all-cause mortality; 3) BMI and functional decline; and 4) weight change and all-cause mortality among older persons. Chapters 3 and 4 detail the results of objectives 1 and 2, respectively. Chapter 5 presents the findings from objective 3, using conditional inference tree analysis – a data mining approach – to construct a risk stratification algorithm for risk of developing functional decline. Chapter 6 addresses objective 4 through a meta-analysis of observational cohort studies on the association between weight change and all-cause mortality. The content presented in Chapter 6 has been published in the *Journal of Nutrition in Gerontology and Geriatrics*. Tables, figures, and references are located at the end of each chapter.
**Figure 1.1** Flow Chart of Geisinger Rural Aging Study (GRAS) Study Participants

GRAS participants who received primary care at the Geisinger Medical Center and were active in the electronic medical records system between 1/1/2001 to 12/31/2004* (n=6,903)

- Exclusions (n = 2,338)
  - Missing laboratory data (n = 1,566)
  - Missing smoking or alcohol data (n = 772)

GRAS participants included in the final analysis for **objective 1 – chapter 3 (n = 4,565)**

- Exclusion (n = 14)
  - BMI <18.5 kg/m²

GRAS participants included in the final analysis for **objective 2 – chapter 4 (n = 4,551)**

- Exclusions (n = 982)
  - Did not complete baseline questionnaire (n = 974)
  - Died (n = 8)

GRAS participants who had complete baseline (1999-2003) activities of daily living (ADL) and instrumental activities of daily living (IADL) data (n=3,583)

- Exclusion (n = 261)
  - Had baseline functional limitation (i.e., indicated having any of the ADL or IADL item)

GRAS participants who had no baseline (1999-2003) functional limitation (n = 3,322)

- Exclusions (n = 1,371)
  - Did not complete follow-up questionnaire (n = 598)
  - Died (n = 773)

GRAS participants who had complete follow-up (2009-2011) activities of daily living (ADL) and instrumental activities of daily living (IADL) data in 1999-2003 and were included in the final analysis for **objective 3 – chapter 5 (n = 1,951)**

*Active was as defined by having at least one outpatient diagnosis and complete basic information (age, sex, weight, and height) during this baseline period.
REFERENCES


Chapter 2

REVIEW OF THE LITERATURE
This section of the dissertation presents a review of the literature on the associations between 1) body mass index (BMI) and all-cause mortality, with particular focus on the “obesity paradox”; 2) the joint effects of BMI and metabolic health status on all-cause mortality; 3) BMI and functional decline; and 4) weight change and all-cause mortality among older persons.

INTRODUCTION

Older adults are among the fastest growing segment in the United States population. The percentage of individuals aged 65 or older is expected to increase from 13.7% in 2012 to 20.9% by 2050 (1). The obesity epidemic continues to grow across all age groups, including older persons. In the United States, approximately 71% of adults aged 60 years or older are either overweight or obese (BMI 25 kg/m² or above); about 31% of them are obese (BMI 30 kg/m² or above) (2). In fact, not only are overweight and obesity common among older individuals, but the rate of increase in prevalence is also similar to that of younger adults (2). Although the percentage of overweight/obese individuals and its rate of increase may be similar across different age groups, age-related changes may modify the association between body weight (i.e., BMI) and health outcomes among younger or middle-aged adults versus older adults.

To better understand the association between overweight/obesity and health outcomes among older persons, it is important to highlight some of the changes that typically occur as part of aging. Older adults tend to have decreased appetite and intake; the mean daily energy intake could decrease by up to 30% from 20 to 80 years old (3,4). This “anorexia of aging” could be due to a number of factors, such as decreased hedonic
motivation to eat and increased concentrations of satiating hormone (e.g., cholecystokinin) (5). However, it is important to note that this phrase or concept may be more appropriate to describe hospitalized frail older persons because studies among healthy older adults have reported conflicting findings (6).

On the other hand, older persons tend to have lower basal metabolic rate as a result of loss of muscle mass (e.g., sarcopenia) (6). Adults aged 65 years or older are estimated to lose up to 0.65 kilograms (kg) per year despite increasing total body fat, especially abdominal adiposity (7,8). Although excess fat, particularly visceral adiposity, is strongly associated with adverse health outcomes (e.g., insulin resistance, diabetes mellitus, and cardiovascular diseases) among younger and middle-aged adults, excess adiposity may have less of a negative impact among older individuals. For example, one study (9) observed that the lipolytic activity of intra-abdominal omental fat, which contributes to insulin resistance and morbidity, is less activated by noradrenaline among older persons (8). Along with these age-related changes, studies have suggested that while elevated BMI increases unfavorable health outcomes among younger individuals (10), overweight or mild obesity may confer no additional (or even lower) all-cause mortality risk than desirable weight among the elderly (11–15). Nevertheless, the explanation for this “obesity paradox” remains unclear and this observation has generated much controversy.

**BODY MASS INDEX AND ALL-CAUSE MORTALITY**

BMI is often used as a proxy to characterize obesity in both clinical and public health settings (16). Although it is not a perfect measurement of adiposity, its convenience, compared to other anthropometric assessments (e.g., body fat mass), has
made it more attractive from both time and cost standpoints. According to the National Institutes of Health (NIH) BMI guidelines, adults aged 20 years or older with a BMI between 18.5 and 24.9 kg/m² are classified as having desirable weight; those with a BMI between 25 and 29.9 kg/m² are classified as overweight; and those with a BMI of 30 kg/m² or over are classified as obese (16). The obese group can further be divided into three levels: obese class I (BMI 30 to 34.9 kg/m²), obese class II (BMI 35 to 39.9 kg/m²), and obese class III (BMI 40 kg/m² or over) (16).

Higher BMI is strongly associated with unfavorable health consequences among young and middle-aged adults. For example, in the Republic of Ireland National Survey of Lifestyle, Attitudes, and Nutrition Study of 10,354 adults aged 18 years or older, obese women had nearly four times (95% CI: 2.5, 6.3) the risk for having diabetes compared to other women with a BMI between 18.5 and 24.9 kg/m² in this cross-sectional study (10). Similar associations also have been noted with other chronic diseases, such as hypertension, lower back pain, sleep apnea, pulmonary dysfunction, osteoarthritis, and cardiovascular diseases (10,17).

Although there is a strong association between obesity and negative health outcomes among younger individuals, there is a growing body of literature (11–15,18) that supports the obesity paradox among older adults. This paradox describes a lower all-cause mortality risk among overweight and even mildly obese (class I obesity) older persons, compared to those with what is currently considered desirable BMI. Among older adults, the U-shaped BMI-mortality curve appeared less pronounced and right-shifted, suggesting a wider “desirable” BMI range (18). Flegal et al. (15) conducted a large systematic review and meta-analysis study on the association between BMI and all-
cause mortality risk across all age groups with a sample size of almost 3 million
individuals and over 270,000 deaths. Relative to desirable weight, the hazard ratios (HR)
for overweight, class I obesity, and class II or III obesity were 0.94 (95% CI: 0.91, 0.96),
0.95 (95% CI: 0.88, 1.01), and 1.29 (95% CI: 1.18, 1.41), respectively (15). Among
adults aged 65 years or older, those with overweight or obesity were not at a significantly
higher risk for all-cause mortality (overweight – HR: 0.90; 95% CI: 0.86, 0.94; class I
obesity – HR: 0.87; 95% CI: 0.72, 1.05; class II or III obesity – HR: 1.20; 95% CI: 0.94,
1.52) (15).

Similar findings also have been observed in other individual studies. The
Established Populations for Epidemiologic Studies of the Elderly included 12,725
participants (8359 non-Hispanic white Americans, 1931 African Americans, and 2435
Mexican Americans) aged 65 years or older (mean age 73 years) over a 7-year follow-up
period (14). The authors (14) reported that overweight (HR: 0.78; 95% CI: 0.72, 0.85)
and class I obese (HR: 0.80; 95% CI: 0.72, 0.90) individuals were at a lower mortality
risk, relative to those with a BMI between 18.5 and 24.9 kg/m² (14). These results were
independent of age, sex, race/ethnicity, education level, marital status, smoking status,
comorbidity, and Established Populations for Epidemiologic Studies of the Elderly site
(14). Similarly, the Longitudinal Study of Aging with 7,260 participants aged 70 years or
older (mean age 76.8 years) found that the lowest HRs were between a BMI of 30 and 35
kg/m² for women and a BMI of 27 and 30 kg/m² for men (13). These analyses also were
adjusted for age, sex, race, education level, income, and other related factors that may be
associated with BMI and all-cause mortality. All of these findings are in line with a
recent meta-analysis by Winter et al. of 32 prospective cohort studies among 197,940
community-dwelling adults aged 65 years or older with a mean follow-up period of 12 years (11). These authors (11) conducted a restricted cubic spline analysis and observed that – relative to a BMI of 23.5 kg/m² – the lowest all-cause mortality risk was between a BMI of 27 and 27.9 kg/m² (HR: 0.90; 95% CI: 0.88, 0.92). This mortality risk began to increase at a BMI less than 23 kg/m² (e.g., BMI 22.0-22.9 – HR: 1.05, 95% CI: 1.05, 1.06) and at a BMI 33 kg/m² or greater (e.g., BMI 33.0-33.9 – HR: 1.08, 95% CI: 1.00, 1.15).

Although numerous investigations (11–15,18) have observed the obesity paradox among older populations, there is still great controversy surrounding this phenomenon. Some researchers raised methodological concerns as potential explanations for the obesity paradox. For example, information bias due to self-reported health data, such as height, weight, disease burden, could underestimate the true effects of obesity on all-cause mortality risk (19). Furthermore, including cigarette smokers could also confound the association between BMI and all-cause mortality because smokers tend to be leaner and die earlier (20). In the National Institutes of Health–American Association of Retired Persons Diet and Health Study of over half a million individuals aged 50 to 71 years in a 10-year follow-up period (21), there was a U-shaped BMI-mortality curve with the lowest all-cause mortality risk among men with a BMI between 25 and 26.4 kg/m² (men – HR: 0.95; 95% CI: 0.91, 0.98) or a BMI between 26.5 and 27.9 kg/m² (men – HR: 0.95; 95% CI: 0.92, 0.98), relative to a BMI between 23.5 and 24.9 kg/m². Yet, when the analysis was restricted to men who never smoked, the association between BMI and all-cause mortality became more monotonic (i.e., BMI 25 to 26.4 kg/m² – HR: 0.97; 95% CI:
0.89, 1.05; BMI 26.5 to 27.9 kg/m² – HR: 1.09; 95% CI: 1, 1.18) (21). Similar findings also were noted among female participants (21).

Other studies, however, continued to observe the obesity paradox even when their analyses excluded those who had ever smoked (12,22). Based on the National Health and Nutrition Examination Survey (12) – relative to a BMI from 18.5 to 24.9 kg/m² – the HRs of all-cause mortality for overweight and class I obesity were 0.95 (95% CI: 0.8, 1.13) and 1.13 (95% CI: 0.89, 1.42), respectively, among participants aged 60 to 69 years old, and 0.91 (95% CI: 0.83, 1.01) and 1.03 (95% CI: 0.91, 1.17), respectively, among individuals aged 70 years or older. Results remained consistent among those who had never smoked (12). For instance, the HRs of all-cause mortality for a BMI between 25 and 29.9 kg/m² and a BMI between 30 and 34.9 kg/m² were 0.81 (95% CI: 0.56, 1.16) and 1.21 (95% CI: 0.83, 1.77), respectively, among participants aged 60 to 69 years old, and 0.90 (95% CI: 0.79, 1.04) and 1.13 (95% CI: 0.96, 1.31), respectively, among individuals aged 70 years or older (12).

Another crucial methodological issue is reverse causation due to early deaths, disease burden, and smoking (20). An individual may be leaner because of underlying illness or condition. In this case, lower BMI (e.g., BMI 18.5-24.9 kg/m²) is the end result of the illness rather than a cause, resulting in a spurious association between BMI and all-cause mortality (20). In addition, many studies have followed the NIH BMI guidelines (e.g., desirable BMI = 18.5 to 24.9 kg/m²), using the cut-off points that were originally developed based upon findings for younger and middle-aged adults, to model BMI (23). In this context, treating BMI as a continuous variable may offer more precise estimates of the relationship between BMI and mortality (24). Therefore, it is imperative to conduct
an analysis that could simultaneously address the aforementioned methodological issues prior to reconsidering whether the current NIH BMI guidelines are appropriate for the older population.

**IMPACT OF BODY MASS INDEX AND METABOLIC HEALTH STATUS ON ALL-CAUSE MORTALITY**

Obesity has long been linked to unfavorable cardiovascular and metabolic health risks (25). However, recent studies suggest that some overweight or obese individuals do not exhibit such adverse health consequences. In 2008, Wildman and colleagues reported that 76.5%, 51.3%, and 31.7% of those who were desirable weight, overweight, and obese, respectively, were metabolically healthy in a nationally representative cohort of United States adults aged 20 years or older (mean age 45 years old) (26).

Multiple studies have examined how the joint effects of BMI and metabolic health status relate to future health outcomes (e.g., all-cause mortality) among younger and middle-aged individuals. In the Health Survey for England and Scottish Healthy Survey with 22,203 individuals (mean age 54.1 years) over a mean 7 years of follow-up, Hamer et al. (27) found that metabolically healthy obese individuals had a HR of 0.91 (95% CI: 0.64, 1.29) for mortality compared with metabolically healthy non-obese participants. These results were adjusted for age, sex, smoking status, physical activity, socioeconomic class, and BMI. Similar findings also have been noted in the Women’s Ischemia Syndrome Evaluation Study of 12,219 women with a mean age of 58 years and a shorter follow-up (i.e., 3 years) (28). After adjusting for age, race, chronic obstructive pulmonary disease, myocardial infarction, congestive heart failure, number of lesions with ≥50%
stenosis, and physical activity level, those who were overweight and obese with healthy metabolic status had HRs of 0.83 (95% CI: 0.15, 4.63) and 0.66 (95% CI: 0.07, 6.01), respectively, for mortality, relative to their counterparts with a BMI between 18.5 and 24.9 kg/m² (28). Durward et al. (29) also did not observe higher all-cause mortality risk among metabolically healthy obese individuals, relative to metabolically healthy desirable weight (18.5-24.9 kg/m²) participants, in the National Health and Nutrition Examination Survey of 4,373 adults with a mean age of 37 years and over an average 14.7 years of follow-up.

In contrast, in the Uppsala Longitudinal Study of Adult Men with 1,758 participants (mean age of 50 years) over a median 30 years of follow-up, Arnlov et al. (30) reported significantly higher risk of all-cause mortality among overweight (HR: 1.21; 95% CI: 1.03, 1.40) and obese (HR: 1.65; 95% CI: 1.03, 2.66) participants without metabolic syndrome, compared to those who were metabolically healthy and at a desirable weight. These analyses were adjusted for age, smoking status, and low density lipoprotein cholesterol (LDL). A meta-analysis study concluded that metabolically healthy overweight (pooled relative risk (RR): 1.10; 95% CI: 0.90, 1.24) and obese (pooled RR: 1.19; 95% CI: 0.98, 1.38) adults are at higher risk, although not significantly, for cardiovascular events and/or all-cause mortality, relative to metabolically healthy desirable weight individuals (31). However, this conclusion may be an artifact of methodological issues and heterogeneity of the design and quality of the included studies. Furthermore, the authors of the meta-analysis paper pooled unadjusted estimates from each study. Thus, the pooled RRs may be prone to residual confounding by smoking and reverse causation by underlying illness.
In addition, as noted by Stefan et al. (32), there is a lack of consensus about how researchers define “metabolically unhealthy.” The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition is commonly used because the required measurements are more feasible to obtain in both clinical and public health settings (33). Based on the NCEP ATP III definition, individuals are considered metabolically unhealthy if they meet three or more of the five criteria: 1) waist circumference > 40 inches (men) or > 35 inches (women); 2) fasting blood glucose ≥ 100 milligrams per deciliter (mg/dl) or diabetes; 3) triglycerides ≥ 150 mg/dl; 4) high-density lipoprotein cholesterol (HDL) < 40 mg/dL (men) or < 50 mg/dL (women); and 5) blood pressure ≥ 130/85 millimeter of mercury (mm Hg) or hypertension (33,34). However, some studies, such as Kuk et al. (35) and Calori et al. (36), utilized only insulin resistance (e.g., HOMA-IR) as a criterion for metabolic health while others studies, such as Durward et al. (29) and Hinnouho et al. (37), incorporated both the NCEP ATP III guidelines and insulin resistance to classify individuals.

More importantly, current studies (31) have not investigated the joint effects of BMI and metabolic health on all-cause mortality in adults aged 65 years or older. Therefore, it is important to validate this approach among older persons and also to examine this concept in the context of the obesity paradox.

**BODY MASS INDEX AND FUNCTIONAL DECLINE**

While the “obesity paradox” phenomenon may be true in terms of all-cause mortality among older adults, higher BMI has been suggested to be associated with greater risk of functional decline (14,38–42), leading to reduced quality of life and
increased need for health care services (43). Thus, it is imperative to also consider the deleterious impact of elevated BMI on functional decline among older persons.

Most epidemiological studies have used self-reported activities of daily living (ADL) and instrumental activities of daily living (IADL) (44, 45). These ADL and IADL questions include: “I usually or always need assistance with (check all that apply): bathing, dressing, grooming, toileting, eating, walking or moving about, traveling (outside the home), preparing food, and shopping for food or other necessities.” (44, 45) Although they are self-reported measurements, ADLs and IADLs have shown to correlate well with more objective physical performance assessments (46–48). Most studies have defined functional limitation as reporting difficulty with one or more ADL or IADL items (14, 38).

Studies have consistently identified elevated BMI as a risk factor for functional decline (14, 38–42, 49). Among 10,975 community dwelling adults aged 65 years or older who participated in the Medicare Current Beneficiary Surveys, higher BMI (i.e., BMI 30 kg/m² or above) was associated with new or exacerbated ADL or IADL disability in a dose-response manner over a 2-year period (38). These analyses were adjusted for age, smoking status, highest education, comorbidity (e.g., cancer, cognitive impairment, chronic lung disease, and rheumatoid arthritis) (38). Similar results also were noted in the Geisinger Rural Aging Study of 2,634 adults aged 65 years or older (mean age of 71 years) over 3 to 4 years of follow-up. After accounting for other covariates (e.g., age, depression, and polypharmacy), a BMI of 35 kg/m² or higher was associated with a significantly greater risk for functional decline (i.e., either ADL or IADL decline) in both men (odds ratio (OR): 3.32; 95% CI: 1.29, 8.46) and women (OR: 2.61; 95% CI: 1.39,
4.95) (40). In The Established Populations for Epidemiologic Studies of the Elderly with 12,725 adults aged 65 years or older over a 7-year follow-up period, a BMI of 30 kg/m² and higher was significantly associated with greater risk of developing ADL disability (14). These results were independent of age, sex, marital status, smoking status, years of education, and a number of medical conditions (e.g., cancer, hypertension, and diabetes) (14). Interestingly, compared to individuals with a BMI between 18.5 and 24.9 kg/m² (reference – HR: 1), those with a BMI between 25 and 29.9 kg/m² did not have a significantly higher risk of developing ADL disability (HR: 1.02; 95% CI: 0.94, 1.10) (14).

Although literature has consistently reported an association between higher BMI and functional limitation, all of the aforementioned studies relied on traditional regression approaches (14,38–42,49). This type of statistical method lacks the ability to address risk classification questions with complex interactions (50). Moreover, regression analysis is generally not well-equipped to handle issue such as translating results for meaningful clinical application (e.g., clinicians usually identify patients as high or low risk in contrast to the risk ratio as determined by regression methods) (50,51). Therefore, it is helpful to consider the use of a data mining approach, such as conditional inference tree analysis, that could effectively address such concerns.

In brief, conditional inference tree analysis is a non-parametric, tree-structured regression model based on an unbiased recursive partitioning technique (52,53). It provides a tree-based data visualization of the complex interactions among predictors in relation to outcome. This approach could potentially improve translation of results into practice (50).
WEIGHT CHANGE AND ALL-CAUSE MORTALITY

While weight reduction has been shown to improve health outcomes (e.g., diabetes, cardiovascular diseases, and all-cause mortality) (54–57) among middle-aged adults, weight loss may not always confer similar beneficial effects, particularly all-cause mortality for older persons (58). For this reason, most weight loss trials have been restricted to younger and middle-aged adults (57). Of the few trials that recruited individuals aged 60 years or older, the results in terms of all-cause mortality were equivocal (59–61). One study (59) observed a significant benefit for weight loss, the other study (60) reported a non-significant benefit for weight loss, and the last study (61) did not find a difference. However, it is important to note that other weight reduction studies with older persons have shown improvements in diabetes, coronary heart disease, and functional status (62). Thus, it would be helpful to further investigate this issue from an epidemiologic standpoint to gather more evidence before investing in clinical trials.

Similar to the definition of metabolic health, there is a lack of a standard weight change terminology. According to the Institute of Medicine, weight loss is defined as “losing at least 5% of body weight, or reducing body mass index (BMI) by at least 1 unit, and keeping weight below this minimum amount for at least 1 year.” (63,64) However, most studies have calculated and defined weight change differently according to the nature of the data. For instance, Amador et al. (65) and Dahl et al. (66) calculated weight change in percentage and defined weight loss as ≥ -5% from baseline, while Ho et al. (67) and Luchsinger et al. (68) calculated weight change in kg and defined weight loss as > -2 kg over 2 years and > -1 kg/year, respectively. Moreover, others, such as Keller et al. (69), calculated weight change in BMI and defined weight loss as ≥ -2 BMI units over a
5-year period. Similar variation is also noted in characterization of weight gain (65–78) and weight fluctuation (73,78,79).

A number of reviews (80–83) has investigated weight change and all-cause mortality. Andres et al. (83) reviewed 13 publications and concluded that those who had lost and gained extreme weight had greater mortality rates, while those who gained small amount of weight had the lowest mortality rates. In contrast, a meta-analysis study conducted by Harrington et al. (81) reported a neutral effect of intentional weight loss on all-cause mortality (pooled RR: 1.01; 95% CI: 0.93, 1.09). Interestingly, the authors observed beneficial effect of weight loss among those who were unhealthily obese (pooled RR: 0.84; 95% CI: 0.73, 0.97) but not among those who were healthily obese (pooled RR: 1.02; 95% CI: 0.91, 1.15) (81). Similarly, Simonsen et al. (82) found three that reported greater all-cause mortality with intentional weight loss, two studies that reported lower all-cause mortality, and four other studies that reported no significant relationships between intentional weight loss and all-cause mortality. Thus, the authors concluded that “it is still not possible for health authorities to make secure recommendations on intentional weight loss.” (82). Poobalan et al. (80) reviewed 11 publications from 8 studies and concluded that there may be some evidence to support the idea that intentional weight loss is beneficial for diabetics and women, but that more studies are needed for men. These mixed results may be due to the inclusion of both younger and older adults in these reviews as age could modify the association between weight and health outcomes (84). Moreover, most of these studies have focused on weight loss and not weight gain or fluctuation.
Therefore, there is a need to conduct a meta-analysis of observational cohort studies to examine current literature on the association between weight change (weight loss, weight gain, and weight fluctuation) and all-cause mortality among older adults. It is also important to conduct multiple subgroup analyses (e.g., age, follow-up length, geographical region, study quality, and sex) to investigate whether those study characteristics could explain some of the heterogeneity in the results.
REFERENCES


Chapter 3

BODY MASS INDEX AND ALL-CAUSE MORTALITY

AMONG OLDER ADULTS
ABSTRACT

Background: Whether the obesity paradox, which describes a lower mortality risk among overweight or mildly obese individuals, exists among older adults remains controversial due to methodological issues.

Objective: To examine the association between baseline body mass index (BMI, kg/m²) and all-cause mortality in a well characterized cohort of older persons.

Methods: We investigated the association between BMI, based on measured height and weight, and all-cause mortality using 4,565 Geisinger Rural Aging Study participants with baseline age 74.0±4.7 (mean±SD) and BMI 29.5±5.3 over a mean of 10.9±3.8 years of follow up.

Results: The relationship between BMI and all-cause mortality was found to be U-shaped (P-non-linearity<0.001). Controlling for age, sex, smoking, alcohol, laboratory values, medications, and comorbidity status, underweight (BMI<18.5) individuals had significantly greater adjusted risk of all-cause mortality than persons of BMI 18.5-24.9 (reference range). Participants with overweight (BMI 25.0-29.9) and class I obesity (BMI 30.0-34.9) had significantly lower adjusted-risk of all-cause mortality. Those with classes II/III obesity (BMI≥35.0) did not have significantly greater adjusted-risk of all-cause mortality. Findings were consistent using propensity score weights and among never-smokers with 2-and 5-year lag analysis and among those with no identified chronic disease.

Conclusions: There is a U-shaped association between BMI and all-cause mortality with lower risk among older persons with overweight and class I obesity in comparison to those with BMI 18.5-24.9.
INTRODUCTION

In the United States, the percentage of individuals aged 65 and older is expected to increase from 13% in 2010 to 20% by 2050 (1). Among this older population, approximately 71% of them evidence overweight or obesity according to the National Institutes of Health (NIH) guidelines (2–4). Greater all-cause mortality risk associated with overweight and obesity is well documented among young and middle-aged adults (5), but among older persons (i.e., age ≥ 65 years) a lower mortality risk has been observed for those with overweight (body mass index, BMI 25.0-29.9 kg/m²) (6,7) and for those with class I obesity (BMI 30.0-34.9) there may be no greater mortality risk compared to those with BMI 18.5-24.9 (8–10).

Although multiple studies (6–10) have supported the obesity paradox of aging, great controversy remains due to methodological issues. These include potential information bias with using self-reported information, such as weight, height, and disease status, residual confounding by smoking, and reverse causation due to early deaths, disease burden, and smoking. These concerns may result in underestimation of the “true” effects of obesity on mortality risk (11). In addition, many studies have used a categorical approach to modeling BMI (e.g., desirable BMI = 18.5-24.9), using the cutoff-points that were originally developed based upon findings for younger and middle-age adults (12). In this context, treating BMI as a continuous variable may offer more precise estimates on the relationship between BMI and mortality (13).

We therefore sought to examine the association between baseline BMI and all-cause mortality in a well characterized cohort of older persons, controlling for age, sex, smoking, alcohol, laboratory values, medications, and comorbidity status. In secondary
analyses, we restricted our analyses to never-smokers without major chronic diseases, excluded early deaths, and used a propensity approach to minimize potential reverse causation and residual confounding. We hypothesized that overweight or class I obesity would not be associated with greater all-cause mortality risk even using these rigorous analytic approaches.
METHODS

Study setting, design, and subjects

The Geisinger Rural Aging Study (GRAS) recruited participants ≥65 years of age residing in northeastern and central Pennsylvania that were enrolled in a Medicare-managed health maintenance organization administered through the Geisinger Health System (Danville, PA). This cohort have been described in detail previously (14). For the present investigation, we evaluated subjects who received primary care at Geisinger Medical Center (Danville, PA) between January 1, 2001 and December 31, 2004 and were active in the electronic medical record (EMR) Epic Systems (Verona, WI). We studied 6,903 individuals that had complete electronic data (i.e., having at least one outpatient diagnosis and complete basic information-age, sex, weight, and height) during this baseline period.

Final analysis included 4,565 participants with 1,566 and 772 individuals excluded for missing laboratory and smoking/alcohol data, respectively (Figure 3.1). Compared to individuals who were included in this study, those who were excluded had greater incidence of mortality over the follow up period (60.5/50.5%) and tended to be slightly older (mean 76.0/74.0 years). BMI (mean 28.7/29.5) and male sex (42.5/41.7%) were however similar. We identified deaths using EMR and the Social Security Death Index data through May 23, 2015.

The Institutional Review Board at the Geisinger Health System approved this study and an IRB-approved Data Sharing Agreement was in place with the Pennsylvania State University.
**Weight, Height, and BMI**

Heights and weights were measured (i.e., without shoes and over-garments) by trained health professionals per standard outpatient clinic visit protocol. We used the earliest plausible height and weight measurements within the baseline time period and applied a strict algorithm to identify implausible and inaccurate values, which were then considered as missing data (15). First, we excluded biologically implausible measurements (height <111.8 centimeters (cm) [<44 inches] or >228.6 cm [>90 inches] and weight <24.9 kilograms (kg) [<55 pounds] or >453.6 kg [>1,000 pounds]) (15). Second, we identified potential inaccurate values by comparing all available measurements for each individual subject (15). We considered any weight measurements as inaccurate if they met one of the two following conditions: 1) the range was >22.7 kg [50 pounds] and the absolute difference between that specific weight and average weight was >70 percent of the range or 2) the standard deviation (SD) was >20% of the average weight and the absolute difference between that particular weight and average weight was greater than the SD. A similar method was employed to detect inaccurate height measurements. We excluded any height values that met the two following conditions: 1) the absolute difference between that particular height and average height was greater than the SD and 2) the SD was >2.5% of the average height. Overall, 0.23% and 2.39% of height and weight measurements, respectively, were considered as implausible or inaccurate. When we detected implausible values, we used the next acceptable value within the baseline period. Because all individuals had ≥1 set of height/weight measurements within the baseline period, no additional subjects were excluded by these steps. Third, we used the earliest plausible heights and weights during the baseline period.
to calculate the BMI, which was classified according to the NIH guidelines: underweight (<18.5), desirable (18.5-24.9), overweight (25.0-29.9), obesity class I (30.0-34.9), obesity class II (35.0-39.9), and obesity class III (≥40.0) (4). We further addressed implausible combinations of height and weight by excluding BMI values <12 or >70 (16). However, none of the BMI measurements fell outside either extreme.

**Assessment of Other Covariates**

Potential confounders were extracted from the EMR. These include age, sex, smoking status (never/former/current smoker), alcohol drinker (yes/no), blood glucose, diabetic medication (yes/no), total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, hypercholesterolemia medication (yes/no), systolic blood pressure (SBP), diastolic blood pressure (DBP), hypertension medication (yes/no) and International Classification of Diseases (ICD)-9. Disease burden, considered as a categorical variable (0, 1, 2, or ≥ 3 diseases), was based on the ICD-9 codes that comprise of the Charlson Index (17). Having 0 disease was identified as free of chronic disease.

We also excluded implausible blood pressure or laboratory values: SBP <60 or >250 mmHg, DBP <40 or >140 mmHg, total cholesterol <65 or >750 mg/dL, HDL cholesterol <10 or >120 mg/dL, LDL cholesterol <30 or >300 mg/dL, blood glucose <30 or >600 mg/dL, and triglyceride <10 or >2000 mg/dL (15,18–21). Because all included participants had ≥1 set of measures within the baseline period, we used the next plausible value within the baseline period if implausible laboratories were detected. Thus, no one was excluded as a result of this step.

To facilitate meaningful subgroup and sensitivity analyses, we constructed three additional variables. Diabetes (22) was defined as having 1) fasting blood glucose ≥ 126
mg/dL or 2) diabetes diagnosis (ICD-9 250.XX). Hypertension (23) was defined as having 1) SBP ≥140 mmHg or DBP ≥90 mmHg or 2) hypertension diagnosis (ICD-9 401.XX-405.XX). Dyslipidemia (24) was defined as having 1) total cholesterol ≥ 200 mg/dL, or 2) triglyceride ≥ 150 mg/dL, 3) HDL cholesterol <50 mg/dL for women or <40 mg/dL for men, or 4) LDL cholesterol ≥ 100 mg/dL or, 5) dyslipidemia diagnosis (ICD-9 272.XX).

**Statistical Analyses**

We calculated hazard ratios (HRs) and associated 95% confidence intervals (CI) for all-cause mortality in relation to BMI categories using Cox proportional hazard models. The reference group was BMI 18.5-24.9. We constructed three multivariate-adjusted Cox models. Model 1 adjusted for age and sex. Model 2 included variables in model 1 and also controlled for smoking status and alcohol use. Model 3 further adjusted for blood glucose, diabetic medication, triglycerides, HDL cholesterol, LDL cholesterol, hypercholesterolemia medication, blood pressure, hypertension medication, and disease burden. We also explored the interactions between BMI categories and covariates, including age (<75/≥75 years), sex, smoking status (never/ever), disease burden (0/≥ 1 conditions), diabetes (yes/no), hypertension (yes/no), and dyslipidemia (yes/no), and conducted associated subgroup analyses. Proportional hazard assumption was examined with Schoenfeld residuals and there was no evidence against this assumption ($P>0.05$) (25,26).

Since there is a nonlinear association between BMI and all-cause mortality (6) and a categorical approach may result in lost information, we also modeled BMI as a continuous variable using restricted cubic spline (27). The appropriate number of knots
was tested by comparing fit statistics (e.g., AIC) and selection of four at the 5th, 25th, 75th, and 95th percentiles of the distribution (28) proved most suitable for our fully-adjusted model (6). We used BMI 23.0, the World Health Organization suggested cut-off point, as the reference value (29).

Furthermore, we conducted four sensitivity analyses. First, we ran a fully-adjusted model among never-smokers with no identified chronic disease burden to minimize reverse causation and potential confounding. Second, we conducted an analysis with propensity score weights that were estimated by generalized boosted models as a different approach to reduce the effects of confounders (30,31). Lastly, among never-smokers, we performed two lag analyses to exclude early deaths that had occurred after two and five years of follow-up to reduce potential reverse causation.

Statistical analyses were performed using SAS 9.4 (SAS Institute; Cary, NC) and level of significance was considered at $P$-value <0.05 (two-tailed).
RESULTS

Baseline Characteristics

This analysis included 4,565 GRAS participants (99.6% Caucasian; mean age 74.0 years [Range, 66.8 to 93.9]; 58.4% women) with a mean baseline of BMI 29.5 (range, 15.6 to 63.5). There were 2,306 deaths over a mean of 10.9 years (range, 0.3 to 14.4 years) of follow up. Age- and sex-adjusted baseline characteristics are shown in Table 3.1. In general, individuals with higher BMI were younger, less likely to be smokers, had greater blood glucose, triglycerides, blood pressure, and disease burden, and lower levels of HDL cholesterol.

Association between BMI and All-Cause Mortality

Underweight individuals had at least two to three times greater all-cause mortality risk than persons of BMI 18.5-24.9 (HR’s ranged from 2.72-3.35; \( P \leq 0.01 \) for all three models) (Table 3.2). Participants with overweight had significantly lower risk of all-cause mortality in all three models (HR’s ranged from 0.80 to 0.84; \( P \leq 0.01 \) for all) (Table 3.2). Those with class I/II obesity did not have significantly greater risk of all-cause mortality in all three models (obesity class I: HR’s, 0.78-0.91; \( P \leq 0.01-0.14 \); obesity class II: HR’s, 0.96-1.13; \( P = 0.14-0.58 \)) while those with class III obesity had significantly greater risk of all-cause mortality in models 1 and 2 (HR’s 1.46-1.55; \( P \leq 0.01 \) for models 1 and 2). Further adjustment for laboratory and comorbidity information in model 3 attenuated this association (HR, 1.17; 95% CI, 0.93-1.47). As expected, the relationship between BMI and all-cause mortality was found to be U-shaped (\( P \)-non-linearity < 0.001). With BMI 23.0 as the reference value, the nadir of the curve (i.e., BMI
range associated with significantly lower mortality risk) was between 23.3 and 36.0 and lowest risk was between 28.0 and 30.0 (Figure 3.2).

**Subgroup Analyses**

Although there were significant interactions between BMI and several covariates (sex, smoking status, disease burden, and dyslipidemia) ($P$-Interaction ≤ 0.05 for all), the U-shaped BMI-mortality curve persisted in all subgroups with lower all-cause mortality risk among those with overweight or class I obesity compared to those with BMI 18.5-24.9 (Table 3.3).

**Sensitivity Analyses**

Including only never-smokers with no identified chronic disease burden or using propensity score weights did not change our findings appreciably. For instance, relative to BMI 18.5-24.9, the HR’s for all-cause mortality for overweight and class I obesity were 0.89 (95% CI, 0.60-1.31) and 1.02 (95% CI, 0.66-1.59), respectively, among never smokers with zero disease burden (n=807), and 0.85 (95% CI, 0.75-0.96) and 0.78 (95% CI, 0.67-0.91), respectively, when using propensity score weights. These findings also persisted with lag analysis among never-smokers. Relative to those with BMI 18.5-24.9, individuals with overweight and class I obesity had HR’s of 0.91 (95% CI, 0.76-1.08) and 0.85 (95% CI, 0.70-1.04), respectively, in the 2-year lag analysis (n=2,555), and 0.89 (95% CI, 0.73-1.08) and 0.85 (95% CI, 0.68-1.05), respectively, in the 5-year lag analysis (n=2,371).
DISCUSSION

In this prospective cohort study of older adults, we observed a U-shaped association between BMI and all-cause mortality with lower risk among those with overweight and mild obesity (class I obesity) and greater risk among persons with underweight and severely obesity (class III obesity), compared to those with BMI 18.5-24.9. Results remained similar while controlling for additional covariates (in all three models), subgroup analyses, and sensitivity analyses, providing additional evidence supporting prior reports for the obesity paradox among older persons. These findings suggest that residual confounding by smoking, and reverse causation due to early deaths, disease burden, and smoking could not fully explain our results.

The lower all-cause mortality risk among persons with overweight or class I obesity found in the present study is consistent with other studies that have focused on older populations (6–9). The Established Populations for Epidemiologic Studies of the Elderly with a mean participant age of 73 years also found that overweight (HR, 0.78; 95% CI, 0.72-0.85) and obesity class I (HR, 0.80; 95% CI, 0.72-0.90) were at lower mortality risk, relative to BMI 18.5-24.9 (9). The Longitudinal Study of Aging with participants ≥70 years found that the lowest HR’s were between BMI 27.0-30.0 for men and 30.0-35.0 for women (8). Similarly, our findings suggest a possible sex-difference (P-interaction: 0.03) with the lowest HR’s observed in the overweight range among men and in the obese class I range among women (Table 3.3). Winter et al. conducted a meta-analysis (6) of prospective cohort studies among community-dwelling adults ≥65 years using restricted cubic spline and reported the lowest all-cause mortality risk was between BMI 27.0 and 27.9 and this risk began to increase at BMI less than 23.0 (reference BMI
value = 23.5). These findings are comparable to our own. It has been suggested that the U-shaped BMI-mortality curve is shifted to the right with aging (32). When examining BMI as a continuous variable, we found the lowest HR’s for all-cause mortality were between 27.0 and 29.0 for adults younger than 75 years and between 29.5 and 31.5 for adults ≥75 years, though this interaction did not reach significance ($P$-interaction: 0.28). In an effort to control for residual confounding and reverse causation, previous studies, including ours, have excluded individuals who smoked, had underlying diseases, or suffered early deaths (6–9). However, the U-shaped BMI-mortality curve for older persons remains unchanged.

There are several potential mechanisms to explain the observed association between BMI and all-cause mortality (11). First, excess fat could lower osteoporotic fracture risk as a result of greater bone mineral density and serve as a protective padding during falls (33). Second, excess fat could act as a metabolic reserve during illness or injury (11). Third, older individuals may be less affected by excess adiposity because of lower noradrenaline-stimulated lipolytic activity in visceral fat, which contributes to insulin resistance and morbidity, as age increases (34). Fourth, physicians may prescribe more aggressive treatments or be more diligent during surgery among those persons with overweight and obesity, which may indirectly contribute to the obesity paradox (35). Fifth, BMI has been suggested as a poor assessment of adiposity among older adults. However, Al Snih et al. called this suggestion into question by showing “the same methods that found little association between elevated BMI and subsequent mortality found a strong association between elevated BMI and disability” (9). Sixth, selective survival could have attenuated the association between higher BMI and all-cause
mortality because those who more affected by excess adiposity may have died at younger ages (11).

There are several strengths to the study that we have conducted. First, we utilized a comprehensive and rigorous algorithm to detect implausible and inaccurate anthropometric and laboratory values. Second, we addressed some important methodological issues that surround the obesity paradox phenomenon by: 1) using weights and heights that were measured by health professionals and diagnosis, laboratory, and medication data (e.g., ICD-9 codes) that were extracted from the EMR to reduce potential information bias, 2) using propensity score weights and conducting subgroup analyses to minimize residual confounding, 3) excluding smokers with underlying disease, and 4) excluding deaths that occurred during the first 2 and 5 years of follow-up to reduce potential reverse causation. Third, we categorized BMI according to the NIH guidelines but also treated it as a continuous variable to provide more precise estimates.

Several limitations should be considered when interpreting our findings. First, we explored the association between all-cause mortality and BMI, not body composition or other anthropometric measurements. While more specific measures of obesity, such as body fat mass, can be powerful predictors of all-cause mortality, most of them are not feasible to implement in routine clinic or community assessments. Thus, exploring the relationship between BMI and all-cause mortality is appropriate from a public health standpoint. Similarly, we focused our outcome on all-cause mortality and not on other health outcomes, such as functional ability or cause-specific mortality, which may have different associations with BMI (36,37). Second, the majority of our participants were
Caucasians from rural Pennsylvania who were of advanced age. Hence, our results may not be generalizable to younger populations or other more diverse groups of older persons. However, the majority of the individuals in the GRAS cohort had BMIs in the overweight and obese categories comparable to those of other populations of older adults (2,3,8,9). Also, the homogeneous nature of the GRAS cohort could be advantageous in helping to minimize potential cohort effects and confounding due to social, health care, and racial disparities.

CONCLUSIONS

Overall, we observed a U-shaped association between BMI and all-cause mortality with lower risk among older persons with overweight and class I obesity. It is important to highlight that our findings cannot be extended to younger or middle aged adults and in no way suggest that older adults with BMI 18.5-24.9 should gain weight. Emphasis should be placed on identifying the characteristics that discern survivors with overweight and mild obesity from non-survivors to better assist health professionals in detecting at-risk individuals for early treatment. For example, recent findings from Murphy and colleagues (38) suggest that those older persons with overweight and mild obesity that exhibit survival advantage do not manifest sarcopenia. Lastly, obesity does not generally confer mortality or health benefits, but our findings suggest there should be priority to reconsider whether the current NIH BMI guidelines are appropriate for application to older persons and whether age-specific recommendations may be indicated.
REFERENCES


Table 3.1 Baseline Characteristics by Body Mass Index Category (n=4,565)a

<table>
<thead>
<tr>
<th>Body Mass Index (kg/m²)</th>
<th>Underweight: &lt;18.5</th>
<th>Desirable: 18.5-24.9</th>
<th>Overweight: 25-29.9</th>
<th>Obese Class I: 30-34.9</th>
<th>Obese Class II: 35-39.9</th>
<th>Obese Class III: ≥40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n)</td>
<td>14</td>
<td>832</td>
<td>1,866</td>
<td>1,202</td>
<td>480</td>
<td>171</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>17.3 ± 0.4</td>
<td>23.0 ± 0.1</td>
<td>27.6 ± 0.0</td>
<td>32.1 ± 0.0</td>
<td>37.0 ± 0.1</td>
<td>44.3 ± 0.1</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>75.3 ± 1.2</td>
<td>74.7 ± 0.2</td>
<td>74.4 ± 0.1</td>
<td>73.6 ± 0.1</td>
<td>73.1 ± 0.2</td>
<td>71.8 ± 0.4</td>
</tr>
<tr>
<td>Men, %</td>
<td>28.4</td>
<td>35.0</td>
<td>45.9</td>
<td>44.6</td>
<td>34.9</td>
<td>24.3</td>
</tr>
<tr>
<td>Smoking Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never, %</td>
<td>26.6</td>
<td>51.0</td>
<td>54.7</td>
<td>52.9</td>
<td>54.0</td>
<td>57.1</td>
</tr>
<tr>
<td>Former, %</td>
<td>21.2</td>
<td>31.7</td>
<td>34.5</td>
<td>36.7</td>
<td>38.7</td>
<td>37.5</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>52.2</td>
<td>17.3</td>
<td>10.7</td>
<td>10.3</td>
<td>7.3</td>
<td>5.4</td>
</tr>
<tr>
<td>Alcohol Drinker, %</td>
<td>12.3</td>
<td>31.8</td>
<td>34.4</td>
<td>30.8</td>
<td>25.0</td>
<td>20.8</td>
</tr>
<tr>
<td>Blood Glucose (mg/dL)</td>
<td>97.9 ± 10.1</td>
<td>106.4 ± 1.3</td>
<td>112.1 ± 0.9</td>
<td>118.6 ± 1.1</td>
<td>124.2 ± 1.7</td>
<td>127.5 ± 2.9</td>
</tr>
<tr>
<td>Diabetes, %b</td>
<td>1.3</td>
<td>24.0</td>
<td>30.9</td>
<td>44.0</td>
<td>53.5</td>
<td>63.7</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>187.2</td>
<td>203.8</td>
<td>202.8</td>
<td>200.1</td>
<td>197.7</td>
<td>197.1</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>117.2 ± 26.0</td>
<td>148.3 ± 3.4</td>
<td>174.3 ± 2.3</td>
<td>188.1 ± 2.8</td>
<td>188.1 ± 4.5</td>
<td>187.8 ± 7.5</td>
</tr>
<tr>
<td>HDL Cholesterol (mg/dL)</td>
<td>57.7 ± 3.6</td>
<td>56.1 ± 0.5</td>
<td>51.1 ± 0.3</td>
<td>48.5 ± 0.4</td>
<td>46.1 ± 0.6</td>
<td>45.5 ± 1.0</td>
</tr>
<tr>
<td>LDL Cholesterol (mg/dL)</td>
<td>106.0 ± 9.5</td>
<td>117.4 ± 1.2</td>
<td>116.6 ± 0.8</td>
<td>114.0 ± 1.0</td>
<td>114.4 ± 1.6</td>
<td>112.7 ± 2.7</td>
</tr>
<tr>
<td>Dyslipidemia, %c</td>
<td>71.5</td>
<td>94.6</td>
<td>95.5</td>
<td>96.1</td>
<td>96.6</td>
<td>96.5</td>
</tr>
<tr>
<td>Systolic (mmHg)</td>
<td>135.4 ± 5.1</td>
<td>136.9 ± 0.7</td>
<td>138.7 ± 0.4</td>
<td>139.3 ± 0.5</td>
<td>141.9 ± 0.9</td>
<td>140.9 ± 1.5</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>73.3 ± 2.7</td>
<td>74.7 ± 0.4</td>
<td>75.9 ± 0.2</td>
<td>76.4 ± 0.3</td>
<td>77.1 ± 0.5</td>
<td>77.1 ± 0.8</td>
</tr>
<tr>
<td>Hypertension Status, %d</td>
<td>62.3</td>
<td>77.1</td>
<td>84.0</td>
<td>86.7</td>
<td>92.9</td>
<td>93.0</td>
</tr>
<tr>
<td>Disease Burden%e</td>
<td>1.2 ± 0.4</td>
<td>1.5 ± 0.0</td>
<td>1.5 ± 0.0</td>
<td>1.7 ± 0.0</td>
<td>1.9 ± 0.1</td>
<td>2.2 ± 0.1</td>
</tr>
</tbody>
</table>

a Age- and sex-adjusted means ± standard errors (continuous variables) and percentages (categorical variables).
Diabetes was defined as having 1) fasting blood glucose ≥ 126 mg/dL or 2) diabetes diagnosis (ICD-9 250.XX).

Dyslipidemia was defined as having 1) total cholesterol ≥ 200 mg/dL, or 2) triglyceride ≥ 150 mg/dL, 3) HDL cholesterol <50 mg/dL for women or <40 mg/dL for men, or 4) LDL cholesterol ≥ 100 mg/dL or, 5) dyslipidemia diagnosis (ICD-9 272.XX).

Hypertension was defined as having 1) SBP ≥140 mmHg or DBP ≥90 mmHg or 2) hypertension diagnosis (ICD-9 401.XX-405.XX).

Disease burden, considered as a categorical variable (0, 1, 2, or ≥ 3 diseases), was based on the ICD-9 codes that comprise of the Charlson Index.
<table>
<thead>
<tr>
<th>BMI Category (kg/m²)</th>
<th>Underweight: 18.5-24.9</th>
<th>Desirable: 18.5-24.9</th>
<th>Overweight: 25-29.9</th>
<th>Obese Class I: 30-34.9</th>
<th>Obese Class II: 35-39.9</th>
<th>Obese Class III: ≥40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event/n</td>
<td>12/14</td>
<td>447/832</td>
<td>920/1,866</td>
<td>578/1,202</td>
<td>252/480</td>
<td>97/171</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Model 3</td>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
</tbody>
</table>

Table 3.2 All-Cause Mortality in Relation to Body Mass Index (n=4,565)

- HR denotes hazard ratio and 95% CI denotes 95% confidence interval.
- Model 1 is adjusted for age and sex.
- Model 2 is adjusted for covariates in model 1 plus smoking status (never, former, or smoker) and alcohol drinker (yes or no).
- Model 3 is adjusted for covariates in model 2 plus blood glucose (mg/dL), diabetic medication (yes or no), triglycerides (mg/dL), HDL cholesterol (mg/dL), LDL cholesterol (mg/dL), hypercholesterolemia medication (yes or no), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), hypertension medication (yes or no), and disease burden (0, 1, 2, or ≥ 3 diseases).
Table 3.3 All-Cause Mortality in Relation to Body Mass Index: Subgroup Analyses (n=4,565)\(^a\)

<table>
<thead>
<tr>
<th>Subgroup (event/n)</th>
<th>Underweight: &lt; 18.5</th>
<th>Desirable: 18.5-24.9</th>
<th>Overweight: 25-29.9</th>
<th>Obese Class I: 30-34.9</th>
<th>Obese Class II: 35-39.9</th>
<th>Obese Class III: ≥40</th>
<th>P-F (^b)</th>
</tr>
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<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&lt; 75 (1,211/2,924)</td>
<td>3.54 (1.56-8.05)</td>
<td>Reference</td>
<td>0.75 (0.64-0.90)</td>
<td>0.74 (0.61-0.89)</td>
<td>0.99 (0.80-1.23)</td>
<td>1.18 (0.90-1.55)</td>
<td>0.28</td>
</tr>
<tr>
<td>≥ 75 (1,095/1,641)</td>
<td>3.16 (1.39-7.19)</td>
<td>Reference</td>
<td>0.84 (0.72-0.98)</td>
<td>0.84 (0.70-1.01)</td>
<td>0.86 (0.67-1.12)</td>
<td>1.00 (0.60-1.66)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Men (1,160/1,897)</td>
<td>6.22 (2.27-17.03)</td>
<td>Reference</td>
<td>0.81 (0.69-0.96)</td>
<td>0.85 (0.70-1.03)</td>
<td>1.08 (0.84-1.38)</td>
<td>1.42 (0.95-2.13)</td>
<td>0.03</td>
</tr>
<tr>
<td>Women (1,146/2,668)</td>
<td>2.81 (1.38-5.70)</td>
<td>Reference</td>
<td>0.77 (0.66-0.90)</td>
<td>0.70 (0.59-0.84)</td>
<td>0.85 (0.68-1.05)</td>
<td>1.01 (0.76-1.34)</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never (1,093/2,590)</td>
<td>2.96 (1.09-8.05)</td>
<td>Reference</td>
<td>0.91 (0.77-1.08)</td>
<td>0.85 (0.70-1.03)</td>
<td>1.12 (0.89-1.41)</td>
<td>1.13 (0.83-1.54)</td>
<td>&lt;0.001</td>
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<tr>
<td>Ever (1,213/1,975)</td>
<td>3.88 (1.90-7.92)</td>
<td>Reference</td>
<td>0.70 (0.60-0.82)</td>
<td>0.71 (0.60-0.85)</td>
<td>0.77 (0.62-0.97)</td>
<td>1.15 (0.82-1.61)</td>
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<tr>
<td><strong>Disease Burden</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 condition (292/1,152)</td>
<td>3.68 (1.07-12.70)</td>
<td>Reference</td>
<td>0.85 (0.62-1.16)</td>
<td>0.97 (0.68-1.38)</td>
<td>1.28 (0.82-2.02)</td>
<td>1.75 (0.85-3.59)</td>
<td>0.003</td>
</tr>
<tr>
<td>≥ 1 conditions (2,014/3,413)</td>
<td>2.76 (1.42-5.37)</td>
<td>Reference</td>
<td>0.80 (0.70-0.90)</td>
<td>0.80 (0.69-0.91)</td>
<td>0.94 (0.79-1.12)</td>
<td>1.18 (0.93-1.50)</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (1,305/2,930)</td>
<td>3.32 (1.86-5.93)</td>
<td>Reference</td>
<td>0.81 (0.71-0.93)</td>
<td>0.78 (0.66-0.92)</td>
<td>1.00 (0.80-1.27)</td>
<td>1.35 (0.93-1.96)</td>
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<tr>
<td>Yes (1,001/1,635)</td>
<td>-</td>
<td>Reference</td>
<td>0.75 (0.61-0.93)</td>
<td>0.78 (0.63-0.96)</td>
<td>0.90 (0.70-1.15)</td>
<td>1.09 (0.79-1.49)</td>
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<tr>
<td><strong>Hypertension</strong></td>
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<td></td>
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<td></td>
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<tr>
<td>No (289/679)</td>
<td>3.57 (1.27-10.04)</td>
<td>Reference</td>
<td>0.79 (0.59-1.07)</td>
<td>0.71 (0.49-1.02)</td>
<td>0.58 (0.32-1.07)</td>
<td>2.07 (0.99-4.33)</td>
<td>0.13</td>
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<td>Yes (2,017/3,886)</td>
<td>2.75 (1.36-5.56)</td>
<td>Reference</td>
<td>0.82 (0.72-0.93)</td>
<td>0.80 (0.70-0.92)</td>
<td>0.98 (0.83-1.17)</td>
<td>1.13 (0.89-1.44)</td>
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</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>No (107/198)</td>
<td>4.06 (1.19-13.92)</td>
<td>Reference</td>
<td>0.53 (0.31-0.92)</td>
<td>0.36 (0.18-0.70)</td>
<td>0.19 (0.06-0.60)</td>
<td>0.56 (0.11-2.79)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Yes (2,199/4,367)</td>
<td>2.74 (1.36-5.53)</td>
<td>Reference</td>
<td>0.81 (0.72-0.91)</td>
<td>0.81 (0.71-0.92)</td>
<td>1.02 (0.86-1.20)</td>
<td>1.21 (0.96-1.53)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) HR denotes hazard ratio and 95% CI denotes 95% confidence interval. Adjusted for age, sex, smoking status (never, former, or smoker), alcohol drinker (yes or no), blood glucose (mg/dL), diabetic medication (yes or no), triglycerides (mg/dL), HDL cholesterol (mg/dL), LDL cholesterol (mg/dL),
hypercholesterolemia medication (yes or no), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), hypertension medication (yes or no), and disease burden (0, 1, 2, or ≥ 3 diseases).

\(^b\) \(P-I = P\)-interaction
Figure 3.1 Flow Chart of Study Geisinger Rural Aging Study (GRAS) Participants

GRAS participants who utilized the Geisinger Medical Center as the primary care and were active in the electronic medical records system between January 1, 2001 to December 31, 2004 (n = 6,903)

Exclusions (n = 2,338)
- Missing laboratory data (n = 1,566)
- Missing smoking or alcohol data (n = 772)

GRAS participants included in the final analysis (n = 4,565)

* Active was as defined by having at least one outpatient diagnosis and complete basic information (age, sex, weight, and height) during this baseline period.
Figure 3.2 All-Cause Mortality in Relation to Body Mass Index: Restricted Cubic Spline

HR/estimation denotes hazard ratio and CI denotes confidence interval. Reference body mass index value = 23 kg/m². Adjusted for age, sex, smoking status (never, former, or smoker), alcohol drinker (yes or no), blood glucose (mg/dL), diabetic medication (yes or no), triglycerides (mg/dL), HDL cholesterol (mg/dL), LDL cholesterol (mg/dL), hypercholesterolemia medication (yes or no), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), hypertension medication (yes or no), and disease burden (0, 1, 2, or ≥ 3 diseases).
Chapter 4

METABOLIC HEALTH STATUS AND THE OBESITY PARADOX

IN OLDER ADULTS
ABSTRACT

Background: The explanation for reduced mortality among older persons with overweight or class I obesity compared to those of desirable weight remains unclear.

Objective: To investigate the joint effects of body mass index (BMI) and metabolic health status on all-cause mortality in a cohort of advanced age. To minimize the effects of reverse causality on the potential relation between obesity/metabolic health and mortality, we conducted multiple sensitivity analyses excluding smokers with no identified chronic disease burden and also those who had early deaths.

Methods: Adults aged 74±4.7 (mean±SD) years at baseline (n=4,551) were categorized according to BMI (18.5-24.9, 25.0-29.9, 30.0-34.9, and ≥35.0 kg/m²) and the presence or absence of a metabolically healthy phenotype (i.e., 0 or 1 risk factors based on a modified Adult Treatment Panel III). Metabolically unhealthy was ≥2 risk factors.

Results: There were 2,294 deaths over a mean 10.9 years of follow-up. Relative to metabolically healthy desirable weight, metabolically healthy overweight or class I obesity was not associated with a greater mortality risk (HR 0.90; 95 CI% 0.73-1.13 and HR 0.58; 95 CI% 0.42-0.80, respectively) (P-interaction<0.001). Results remained consistent among never-smokers with no identified chronic disease burden and also with 5-year lag analysis.

Conclusions: The “obesity paradox” may be partially explained by the inclusion of metabolically healthy overweight and obese older persons, who do not have elevated mortality risk, in population studies of BMI and mortality.
INTRODUCTION

Overweight and obesity are strongly associated with adverse health outcomes and all-cause mortality in younger and middle-aged adults (1,2). Yet, among older persons, a substantial literature suggests that the lowest mortality risk may be among the overweight (BMI 25.0-29.9 kg/m²) and that class I obesity (BMI 30.0-34.9) may have no greater risk compared to those with BMI 18.5-24.9 (3–6). Nevertheless, the explanation for this “obesity paradox” in older persons remains unclear and the findings have generated considerable controversy (7–9).

Wildman and colleagues studied metabolic health using a modified Adult Treatment Panel (ATP-III) guideline and found that among adults ≥20 years (mean age 45.0), 76.5%, 51.3%, and 31.7% of those with BMI 18.5-24.9, overweight, and obese were metabolically healthy, respectively (10). While the association between metabolic health and all-cause mortality has been documented among middle-aged adults, this approach has not yet been well validated for older persons (11,12).

We hypothesized that metabolically healthy overweight and class I obesity would not be associated with greater mortality risk and that metabolic health status would modify the association between BMI and mortality in older adults. Our primary objective was to investigate the joint effects of BMI class and metabolic health in relation to all-cause mortality in a well-characterized cohort of older persons. To minimize the effects of reverse causality on the potential relation between obesity/metabolic health and mortality, we conducted multiple sensitivity analyses excluding smokers with no identified chronic disease burden and also those who had early deaths.
METHODS

Study Population

Details regarding the Geisinger Rural Aging Study (GRAS) cohort have been previously published (13). Approximately 6903 GRAS participants received primary care at Geisinger Medical Center (Danville, PA) and were active in the electronic medical record (EMR) Epic Systems (Verona, WI) between January 1, 2001 and December 31, 2004. We limited the analysis to only those participants for this investigation.

We excluded individuals with missing smoking or alcohol information (n=772) or laboratory data (n=1,566). Compared to those who were included in this analysis, those excluded tended to be slightly older (mean 76.3/74.0 years) and had higher incidence of mortality over the duration of follow-up (60.5/50.4%) but female sex (57.5/58.4%) and BMI (mean 28.7/29.6) were similar. For this study, we eliminated those with BMI <18.5 (n=14), so that 4551 participants remained for final analysis. Deaths were identified using EMR and Social Security Death Index data through May 23, 2015.

The study was approved by the Institutional Review Board (IRB) at the Geisinger Health System. There was an IRB-approved Data Sharing Agreement with the Pennsylvania State University.

Classification of BMI and Metabolic Health

Weights and heights of individuals were obtained per standard outpatient clinic visit protocol without over-garments and shoes. The earliest plausible weights and heights between January 1, 2001 and December 31, 2004 were used. A strict algorithm was applied to detect implausible or inaccurate values, which were treated as missing data. First, we eliminated measurements that were implausible (weight <24.9 kg [<55
pounds] or >453.6 kg [>1,000 pounds]; height <111.8 cm [<44 inches] or >228.6 cm
[>90 inches]) (14). Second, we detected potential inaccurate values by comparing all
available measurements for each individual participant (14). Weights were designated
inaccurate if the standard deviation (SD) was >20% of the mean weight and the absolute
difference between a specific weight and mean weight was greater than the SD or the
range was >22.7 kg [50 pounds] and the absolute difference between a specific weight
and mean weight was >70% of the range. To detect inaccurate heights, we excluded
values where the SD was >2.5% of the mean and the absolute difference between a
specific height and mean height was greater than the SD. The overall rates of implausible
or inaccurate weights and heights were 0.23% and 2.39%, respectively. All included
participants had at least one set of anthropometric measurements within the baseline
period. In the case of implausible values, we used the next available value within that
period. Thus, no one was excluded by these steps. Third, we calculated the BMI using the
earliest plausible measurements during the baseline period and would have further
excluded implausible combinations of weight and height by excluding BMI <12 or >70,
but all BMI’s were within this range (15). Lastly, BMI was categorized per the NIH
guidelines: underweight (<18.5), desirable (18.5-24.9), overweight (25.0-29.9), obesity
class I (30.0-34.9), and obesity class II/III (≥35.0) (5,6).

Metabolic health status was defined using a modified ATP-III guideline similar to
that used by Wildman and colleagues (10,16). Participants with 0 or 1 of the following
conditions were considered metabolically healthy: triglycerides ≥1.69 mmol/L (≥150
mg/dL); high density lipoprotein (HDL) cholesterol for women <1.29 mmol/L (<50
mg/dL) or for men <1.03 mmol/L (<40 mg/dL); blood pressure ≥130/85 mm Hg or
hypertension diagnosis (ICD-9 401.XX-405.XX); and fasting glucose ≥5.56 mmol/L (≥100 mg/dL) or diabetes diagnosis (ICD-9 250.XX). The definition did not include lipid ICD-9 codes because there was not an ICD-9 code for low HDL cholesterol and the ICD-9 code for hypertriglyceridemia was not commonly used. Waist circumference was not available. Before identifying the earliest plausible EMR measures within the baseline time period for each individual, implausible values were excluded: systolic blood pressure <60 or >250 mm Hg, diastolic blood pressure <40 or >140 mm Hg, HDL cholesterol <0.26 or >3.10 mmol/L (<10 or >120 mg/dL), blood glucose <1.67 or >33.3 mmol/L (<30 or >600 mg/dL), and triglycerides <0.11 or >22.60 mmol/L (<10 or >2000 mg/dL) (14,17–20). All included individuals had multiple measures within the baseline period, so we used the next available value within that period if implausible values were identified. Thus, no participants were excluded for missing blood pressure or laboratories.

Assessment of Other Covariates

Age, sex, smoking status (never, former, or smoker), alcohol drinker (yes/no), low-density lipoprotein (LDL) cholesterol, medications for hypercholesterolemia, hypertension, and diabetes, and ICD-9 codes, were extracted from the EMR. Disease burden, treated as a categorical variable (0, 1, 2, or ≥ 3 diseases), was calculated using the ICD-9 codes (excluding the codes for diabetes-250.XX) that comprise the Charlson Index (21). Free of identified chronic disease was defined as having zero disease burden. Before identifying the earliest plausible laboratories within the baseline time period for each individual, we excluded implausible LDL cholesterol values of <0.78 or >7.76 mmol/L (<30 or >300 mg/dL) (14).
**Statistical Analyses**

To examine the joint effects of BMI and metabolic health in relation to all-cause mortality, we categorized individuals into 8 exclusive groups corresponding to desirable, overweight, class I, and class II/III BMI categories and metabolic health risk (healthy/unhealthy).

We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause mortality in relation to the 8 groups using Cox proportional hazard models. The reference group was BMI 18.5-24.9 and metabolically healthy. We also examined the joint effects of BMI and individual metabolic risk components in relation to all-cause mortality. Proportional hazards assumption was assessed with Schoenfeld residuals and no evidence against this assumption was found ($P>0.05$) (22,23).

In addition to model 1, which adjusted for age and sex, two other multivariate-adjusted Cox models were constructed. Model 2 included variables in model 1 and was also adjusted for smoking and alcohol use. Model 3 further controlled for LDL cholesterol, hypercholesterolemia drug, and disease burden.

Subgroup analyses were stratified by age (<75/≥75 years), sex, smoking status (never/ever), and disease burden (0/≥1 conditions). Likelihood ratio tests were used to examine statistical interactions between the main exposure and the aforementioned factors on mortality, by comparing $-2 \log$ likelihood $[\chi^2]$ between nested models with and without the cross-product terms of the exposures and tested factors.

Nine sensitivity analyses were conducted and are reported in a supplemental appendix. First, analysis was performed with propensity score weights, estimated by generalized boosted models, to minimize the effects of confounders (24,25). Second, a
fully-adjusted model was run using only never-smokers with zero disease burden to address reverse causation and potential confounding. Third, the metabolic health definition was modified to include all individuals meeting our diabetes criteria as metabolically unhealthy irrespective of other criteria. Fourth, in an effort to have a more “clean” metabolically healthy group, we included only those who did not have any of the above mentioned metabolic risk components. Fifth, to reduce potential reverse causation, we performed analysis among never-smokers, with the exclusion of deaths occurring in the first 5 years of follow-up. Sixth, because metabolic health status could change during the follow up, we also excluded those who became metabolically unhealthy during follow-up. The last three sensitivity analyses relate to medication use; we excluded 1) those who were on cholesterol lowering medications, 2) those without diabetes diagnosis but on diabetics medications, and 3) those without hypertension diagnosis but on blood pressure medications.

Statistical analyses were conducted using SAS 9.4 (SAS Institute; Cary, NC). $P$-value $<0.05$ (two-tailed) was considered significant.
RESULTS

Baseline Characteristics

This study included 4551 GRAS participants (58.4% women; mean age 74.0 [66.8 to 93.9]; 99.6% Caucasian). Mean follow-up was 10.9 years (0.3-14.4). Mortality was 50.4%. See Table 4.1 for baseline characteristics by BMI class and metabolic health. The proportion of metabolically unhealthy persons increased with higher BMI class (Figure 4.1).

All-Cause Mortality by BMI and Metabolic Health

Metabolic health status significantly modified the association between BMI and mortality ($P$-interaction<0.001). Compared to metabolically healthy individuals with BMI 18.5-24.9, class II/III obese persons had significant elevations in mortality risk related to unhealthy metabolic status after adjustment for age and sex (Table 4.2 and Figure 4.2). Further adjustment for smoking, alcohol, laboratories, and comorbidity did not change the results appreciably. Compared to the metabolically healthy with BMI 18.5-24.9, their overweight and obesity class I metabolically healthy counterparts had HRs that tended to be lower, though this trend did not reach significance for the overweight group (Table 4.2 and Figure 4.2). Even those who were metabolically healthy obesity class II/III did not exhibit significantly higher risk than those with BMI 18.5-24.9 (Table 4.2 and Figure 4.2). Findings were also consistent when we included relevant medications in our definition (e.g., glycemic risk as fasting glucose $\geq 5.56$ mmol/L ($\geq 100$ mg/dL) or diabetes diagnosis (ICD-9 250.XX) or evidence of treatment with a diabetes medication), similar to that used by Wildman et al. (10) (data not shown).
Subgroup and Sensitivity Analyses

Results from subgroup analyses detected significant effect modifications based on sex, smoking status, and disease burden (Table 4.3). Metabolically healthy women of BMI 30-34.9 and ≥ 35 had lower HRs for mortality compared to men in the same BMI groups. Furthermore, exclusion of smokers with no identified chronic disease burden or those who had died in the first 5 years of follow-up did not result in findings that were substantially different than those of the primary analysis (Figure 4.2). We also observed consistent patterns when we used propensity scoring, modified our metabolic health definition (see statistical analyses section), excluded those on related medications, and excluded those who were metabolically healthy at baseline and became unhealthy during follow-up (Figure 4.2 and Supplementary Table 1-5 (Table 4.4-4.8)).

Lastly, in comparison to other participants the association between BMI and mortality was more pronounced in those participants with blood glucose ≥5.56 mmol/L (≥100 mg/dL) or a diabetes diagnosis ($P$-interaction=0.03), but not with the other three tested metabolic risk factors (Supplementary Table 1 (Table 4.4)).
DISCUSSION

Our study reveals that metabolic health status significantly modifies the association between BMI and mortality of older persons. Furthermore, compared to the metabolically healthy with BMI 18.5-24.9, the metabolically healthy overweight or obesity class I did not have significantly greater risk of all-cause mortality in all 3 models and subgroup analyses independent of age, sex, smoking, alcohol, laboratories, and comorbidity. We observed similar results in sensitivity analyses, suggesting that residual confounding by smoking and reverse causation by disease burden, early deaths, and smoking could not fully explain our findings.

While U-shaped BMI-mortality curves were found for both metabolically healthy and unhealthy individuals, those who were metabolically healthy tended to have lower HRs suggesting that the “obesity paradox” may be partially explained by the inclusion of metabolically healthy overweight and obese older persons who do not have elevated mortality risk. The greatest survival benefit appears to be among the metabolically healthy class I obese, which may be due to the advanced age of our cohort. It has been previously reported that the U-shaped BMI-mortality curve is shifted to the right as age increases (26). This pattern, however, was not observed among metabolically unhealthy in our investigation. While metabolic health clearly alters the relationship between BMI and all-cause mortality, those with unhealthy metabolic status still exhibit a U-shaped mortality curve. This suggests that there are likely factors in addition to metabolic health that account for the obesity paradox.

To the best of our knowledge, this is one of the first studies to investigate the combination of metabolic risk per modified ATP-III criteria and BMI in relation to all-cause mortality among older persons of advanced age (mean 74 years at baseline).
reduce information bias, we used measured weights and heights obtained by health professionals. We also implemented a rigorous algorithm to detect implausible and inaccurate measures.

Our observations extend upon previous studies of middle-aged adults. Among 22,203 individuals (mean age 54.1 years), Hamer et al (11) found that metabolically healthy obese had a fully adjusted HR of 0.91 (95% CI, 0.64-1.29) for mortality compared with metabolically healthy non-obese. Kip et al (12) found that women (mean age 58 years), who were overweight and obese with healthy metabolic status had adjusted HRs of 0.83 (95% CI, 0.15-4.63) and 0.66 (95% CI, 0.07-6.01) for mortality, respectively, relative to their BMI 18.5-24.9 counterparts (12).

In our study, metabolic health significantly modified the association between BMI and mortality underscoring the importance of taking metabolic risk into consideration with BMI when identifying at risk individuals. Among BMI 18.5-24.9, overweight, obesity class I, and obesity class II/III, the prevalence of healthy metabolic status was 35.2%, 21.5%, 13.6%, and 9.7%, respectively. Thus, weight reduction may not be an appropriate recommendation for many overweight and mildly obese older persons who are metabolically healthy. However, based upon our findings and current evidence (27), older persons with BMI 18.5-24.9, especially those who are metabolically unhealthy, should not be encouraged to gain weight. The mechanisms remain largely unclear for metabolic health among many overweight and obese older persons, but may relate to differences in postprandial response, body composition, and genetic predisposition (28–32).
Our study had a number of limitations. The cohort was comprised almost entirely of Caucasians of advanced age from central/northeastern Pennsylvania. Selection bias is expected as our cohort was comprised of aged individuals and excess mortality associated with unhealthy metabolic status is likely at younger ages. Thus, our findings may not be generalizable to other more diverse or younger populations. However, similar findings have been observed among middle aged individuals of greater diversity (11,12). In addition, the homogeneous nature of our cohort could help to reduce potential confounding due to racial, social, and healthcare disparities. We used a modification of the ATP-III guideline because waist circumference data was of limited availability. Regardless, our findings remained consistent in sensitivity analyses using different metabolic health definitions and are also comparable with other studies (11,12) that used waist circumference. While BMI lacks specificity in differentiating fat and lean body mass, unhealthy metabolic status is positively associated with higher abdominal fat regardless of overall adiposity (33–37). BMI is a more feasible measure for routine screening and it is of practical utility in public health applications. Thus, our findings support the use of EMR metabolic risk data with BMI to better identify individuals at risk for mortality (11,12,38). In addition, we did not have weight loss information at baseline. To address weight loss that may be due to undiagnosed diseases, we performed a 5-year lag analysis but results were consistent. Lastly, some studies suggested that obesity could cause metabolic abnormalities. We thus conducted sensitivity analysis by excluding those who were metabolically healthy at baseline but became unhealthy during follow-up. We obtained similar results.
CONCLUSIONS

In this study, metabolically healthy overweight or obesity was not associated with a significantly greater mortality risk than metabolically healthy BMI 18.5-24.9. In addition, metabolic health status modified the association between BMI and mortality. Therefore, assessment of metabolic health status using a modified ATP-III guideline should be considered across all BMI classes. Combining metabolic health risk with BMI may offer advantage compared to BMI alone in differentiating mortality risk outcomes. Our findings suggest that the “obesity paradox” in previous studies may be partially explained by the inclusion of metabolically healthy overweight and obese persons who do not have an elevated mortality risk. Future studies are warranted to validate our findings in other populations of older persons. Body composition is also an important consideration as any survival advantage is reported to disappear among overweight/mildly obese older persons who also have sarcopenia, while those with intact lean body mass have reduced mortality (39). Future investigation should help to clarify whether overweight/obese older persons with sarcopenia can potentially be identified with a metabolic risk profile.
TAKE AWAY POINTS

- The “obesity paradox” has generated considerable controversy due to methodological issues (i.e., potential reverse causation and residual confounding).

- Based on rigorous sensitivity analyses, our prospective cohort study showed that residual confounding by smoking and reverse causation by disease burden, early deaths, and smoking could not fully explain the “obesity paradox”.

- We found that metabolic health status modified the association between BMI and mortality. Specifically, those who were metabolically healthy overweight or obese did not have a significantly greater mortality risk than those who were metabolically healthy with BMI of 18.5-24.9.

- Our findings suggest that the “obesity paradox” described in previous studies may be partially explained by the inclusion of metabolically healthy overweight and obese persons who do not have an elevated mortality risk.
REFERENCES


Table 4.1 Baseline Characteristics of the Study Population, by Body Mass Index Class (n=4,551)\(^a\)

<table>
<thead>
<tr>
<th>Body Mass Index (kg/m(^2))</th>
<th>18.5-24.9</th>
<th>25.0-29.9</th>
<th>30.0-34.9</th>
<th>≥35.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolically Healthy(^b)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Total (n)</td>
<td>293</td>
<td>539</td>
<td>401</td>
<td>1,465</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>22.8 ± 0.1</td>
<td>23.1 ± 0.1</td>
<td>27.5 ± 0.1</td>
<td>27.7 ± 0.1</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>74.4 ± 0.3</td>
<td>74.8 ± 0.2</td>
<td>74.2 ± 0.2</td>
<td>74.4 ± 0.1</td>
</tr>
<tr>
<td>Men, %</td>
<td>35.4</td>
<td>34.7</td>
<td>48.8</td>
<td>45.1</td>
</tr>
<tr>
<td>Smoking Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never, %</td>
<td>54.2</td>
<td>49.2</td>
<td>58.0</td>
<td>53.8</td>
</tr>
<tr>
<td>Former, %</td>
<td>28.5</td>
<td>33.4</td>
<td>33.1</td>
<td>35.0</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>17.3</td>
<td>17.3</td>
<td>8.9</td>
<td>11.2</td>
</tr>
<tr>
<td>Alcohol Drinker, %</td>
<td>34.4</td>
<td>30.3</td>
<td>37.3</td>
<td>33.6</td>
</tr>
<tr>
<td>Blood Glucose (mmol/L)(^c)</td>
<td>5.1 ± 0.1</td>
<td>6.4 ± 0.1</td>
<td>5.1 ± 0.1</td>
<td>6.5 ± 0.1</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>2.9</td>
<td>29.8</td>
<td>4.5</td>
<td>33.5</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)(^c)</td>
<td>1.2 ± 0.1</td>
<td>1.9 ± 0.0</td>
<td>1.2 ± 0.1</td>
<td>2.2 ± 0.0</td>
</tr>
<tr>
<td>HDL Cholesterol (mmol/L)(^c)</td>
<td>1.7 ± 0.0</td>
<td>1.3 ± 0.0</td>
<td>1.6 ± 0.0</td>
<td>1.3 ± 0.0</td>
</tr>
<tr>
<td>LDL Cholesterol (mmol/L)(^c)</td>
<td>3.0 ± 0.1</td>
<td>3.0 ± 0.0</td>
<td>3.1 ± 0.0</td>
<td>3.0 ± 0.0</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>38.9</td>
<td>60.7</td>
<td>51.2</td>
<td>64.3</td>
</tr>
<tr>
<td>Systolic (mm Hg)(^c)</td>
<td>132.9 ± 1.1</td>
<td>139.1 ± 0.8</td>
<td>133.8 ± 0.9</td>
<td>140.0 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>73.8 ± 0.6</td>
<td>75.2 ± 0.4</td>
<td>75.1 ± 0.5</td>
<td>76.1 ± 0.3</td>
</tr>
<tr>
<td>-------------------------</td>
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<td>------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>52.6</td>
<td>75.6</td>
<td>56.1</td>
<td>82.2</td>
</tr>
<tr>
<td>Disease Burden</td>
<td>1.2 ± 0.1</td>
<td>1.3 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>1.2 ± 0.0</td>
</tr>
</tbody>
</table>

*a* Age- and sex-adjusted means ± standard errors (continuous variables) and percentages (categorical variables).

*b* Metabolically healthy represents having ≤ 1 metabolic components as defined by a modified ATP III criteria.

*c* mmol/L denotes millimoles per liter, mmHg millimeters of mercury, HDL high-density lipoprotein, and LDL low-density lipoprotein.
Table 4.2 All-cause Mortality in Relation to Body Mass Index and Metabolic Status (n=4,551)

<table>
<thead>
<tr>
<th>Body Mass Index (kg/m²)</th>
<th>Metabolically Healthya</th>
<th>Event/n</th>
<th>HR (95% CI)</th>
<th>HR (95% CI)</th>
<th>HR (95% CI)</th>
<th>HR (95% CI)</th>
<th>HR (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5-24.9</td>
<td>Yes</td>
<td>139/293</td>
<td>1.26 (1.03-1.54)</td>
<td>0.87 (0.70-1.08)</td>
<td>1.00 (0.83-1.20)</td>
<td>0.59 (0.43-0.81)</td>
<td>1.13 (0.94-1.37)</td>
<td>0.72 (0.44-1.16)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>308/539</td>
<td>1.22 (1.00-1.49)</td>
<td>0.88 (0.71-1.10)</td>
<td>0.98 (0.81-1.17)</td>
<td>0.60 (0.43-0.83)</td>
<td>1.11 (0.92-1.34)</td>
<td>0.74 (0.46-1.19)</td>
</tr>
<tr>
<td>25.0-29.9</td>
<td>Yes</td>
<td>187/401</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>No</td>
<td>733/1,465</td>
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<tr>
<td>30.0-34.9</td>
<td>Yes</td>
<td>50/164</td>
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<td></td>
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<tr>
<td></td>
<td>No</td>
<td>528/1,038</td>
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<tr>
<td>≥35.0</td>
<td>Yes</td>
<td>19/63</td>
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<tr>
<td></td>
<td>No</td>
<td>330/588</td>
<td></td>
<td></td>
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</tbody>
</table>

a Metabolically healthy represents having ≤ 1 metabolic components as defined by a modified ATP III criteria. HR denotes hazard ratio and 95% CI denotes 95% confidence interval.

b Model 1 is adjusted for age and sex.

c Model 2 is adjusted for covariates in model 1 plus smoking status (never, former, or smoker) and alcohol drinker (yes or no).

d Model 3 is adjusted for covariates in model 2 plus low-density lipoprotein cholesterol, hypercholesterolemia drug (yes or no), and disease burden (0, 1, 2, or ≥ 3 diseases).
Table 4.3 Subgroup Analyses: All-cause Mortality in Relation to Body Mass Index and Metabolic Status

<table>
<thead>
<tr>
<th>Body Mass Index (kg/m²)</th>
<th>18.5-24.9</th>
<th>25.0-29.9</th>
<th>30.0-34.9</th>
<th>≥35.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolically</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>Subgroup (event/n)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age (P=0.58)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&lt; 75</td>
<td>Reference</td>
<td>1.37 (1.01-1.86)</td>
<td>0.86 (0.61-1.21)</td>
<td>1.01 (0.76-1.33)</td>
</tr>
<tr>
<td>≥ 75</td>
<td>Reference</td>
<td>1.10 (0.84-1.45)</td>
<td>0.93 (0.70-1.25)</td>
<td>0.92 (0.72-1.17)</td>
</tr>
<tr>
<td>Sex (P&lt;0.001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>Reference</td>
<td>1.05 (0.78-1.41)</td>
<td>0.79 (0.58-1.07)</td>
<td>0.91 (0.70-1.18)</td>
</tr>
<tr>
<td>Women</td>
<td>Reference</td>
<td>1.37 (1.04-1.81)</td>
<td>1.04 (0.76-1.43)</td>
<td>0.96 (0.74-1.24)</td>
</tr>
</tbody>
</table>
### Smoking Status ($P<0.001$)$^b$

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Reference</th>
<th>Never 1.089/2,585 (1,089/2,585)</th>
<th>Ever 1.205/1,966 (1,205/1,966)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reference</td>
<td>1.46 (1.07-1.98) 1.05 (0.76-1.47) 1.27 (0.96-1.67) 0.52 (0.31-0.90) 1.35 (1.02-1.80) 1.05 (0.56-1.96) 1.79 (1.33-2.41)</td>
<td>1.04 (0.79-1.36) 0.74 (0.55-0.99) 0.73 (0.57-0.93) 0.54 (0.36-0.81) 0.77 (0.60-0.99) 0.49 (0.23-1.07) 0.94 (0.71-1.23)</td>
</tr>
</tbody>
</table>

### Disease Burden ($P=0.04$)$^b$

<table>
<thead>
<tr>
<th>Disease Burden</th>
<th>Reference</th>
<th>0 condition 431/1,517 (431/1,517)</th>
<th>≥ 1 conditions 1,863/3,034 (1,863/3,034)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reference</td>
<td>1.44 (0.88-2.36) 1.24 (0.74-2.08) 1.12 (0.72-1.76) 0.81 (0.37-1.76) 1.49 (0.95-2.36) 1.39 (0.59-3.24) 1.99 (1.23-3.22)</td>
<td>1.18 (0.94-1.47) 0.83 (0.65-1.06) 0.93 (0.76-1.14) 0.52 (0.36-0.74) 1.02 (0.83-1.25) 0.60 (0.33-1.08) 1.26 (1.01-1.57)</td>
</tr>
</tbody>
</table>

$^a$ Metabolically healthy represents having ≤ 1 metabolic components as defined by a modified ATP III criteria. HR denotes hazard ratio and 95% CI denotes 95% confidence interval. Model is adjusted for age, sex, smoking status (never, former, or smoker), alcohol drinker (yes or no), LDL cholesterol, hypercholesterolemia drug (yes or no), and disease burden (0, 1, 2, or ≥ 3 diseases)

$^b$ $P = P$- Interaction.
Figure 4.1 Distribution of Metabolic Risk Factors and Metabolic Health Status by Body Mass Index

Figure 1A - Distribution of Metabolic Risk Factors by Body Mass Index

<table>
<thead>
<tr>
<th>BMI 18.5-24.9</th>
<th>BMI 25.0-29.9</th>
<th>BMI 30.0-34.9</th>
<th>BMI ≥35.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>15.1</td>
<td>21.6</td>
<td>29.6</td>
</tr>
<tr>
<td>3</td>
<td>26.9</td>
<td>31.5</td>
<td>34.4</td>
</tr>
<tr>
<td>2</td>
<td>36.5</td>
<td>33.3</td>
<td>26.3</td>
</tr>
<tr>
<td>1</td>
<td>18.8</td>
<td>11.5</td>
<td>9.1</td>
</tr>
<tr>
<td>0</td>
<td>2.7</td>
<td>2.2</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Figure 1B - Metabolic Health Status by Body Mass Index

Metabolically Healthy | Metabolically Unhealthy
Figure 4.2 All-cause Mortality in Relation to Body Mass Index and Metabolic Status

Figure 2A. All Participants (n = 4,551)

Event/n | HR (95% CI)
---|---
447/832 | 1.0 (Reference)
920/1,866 | 0.80 (0.71-0.90)
578/1,202 | 0.80 (0.71-0.91)
349/651 | 1.06 (0.92-1.23)
139/293 | 1.0 (Reference)
187/401 | 0.90 (0.73-1.13)
50/164 | 0.58 (0.42-0.80)
19/63 | 0.78 (0.48-1.27)
308/539 | 1.24 (1.01-1.52)
733/1,465 | 0.96 (0.80-1.16)
528/1,038 | 1.04 (0.86-1.26)
330/588 | 1.34 (1.10-1.64)

BMI 18.5-24.9  • BMI 25.0-29.9  • BMI 30.0-34.9  ▲ BMI ≥35.0

Figure 2B. Never-Smoker with No Identified Chronic Disease Burden (n=1,046)

Event/n | HR (95% CI)
---|---
18/83 | 1.0 (Reference)
21/107 | 1.11 (0.59-2.09)
5/30 | 0.91 (0.34-2.44)
3/18 | 0.96 (0.28-3.27)
38/117 | 1.69 (0.96-2.97)
80/342 | 1.20 (0.72-2.01)
60/222 | 1.40 (0.83-2.39)
39/127 | 1.88 (1.07-3.31)

BMI 18.5-24.9  • BMI 25.0-29.9  • BMI 30.0-34.9  ▲ BMI ≥35.0
Figure 2C. Never-Smoker, 5-Year Lag Analysis (n=2,367)

<table>
<thead>
<tr>
<th>Event/n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>51/168</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>72/220</td>
<td>1.01 (0.71-1.45)</td>
</tr>
<tr>
<td>13/82</td>
<td>0.46 (0.25-0.84)</td>
</tr>
<tr>
<td>10/40</td>
<td>1.00 (0.51-1.98)</td>
</tr>
<tr>
<td>106/264</td>
<td>1.29 (0.93-1.81)</td>
</tr>
<tr>
<td>275/744</td>
<td>1.17 (0.86-1.58)</td>
</tr>
<tr>
<td>192/521</td>
<td>1.28 (0.94-1.75)</td>
</tr>
<tr>
<td>152/328</td>
<td>1.85 (1.34-2.55)</td>
</tr>
</tbody>
</table>

- ■ BMI 18.5-24.9
- ● BMI 25.0-29.9
- ● BMI 30.0-34.9
- ▲ BMI ≥35.0

Figure 2D. Using a Modified Metabolic Health Definition (n=4,551)

<table>
<thead>
<tr>
<th>Event/n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>136/288</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>177/383</td>
<td>0.88 (0.70-1.10)</td>
</tr>
<tr>
<td>48/158</td>
<td>0.57 (0.41-0.80)</td>
</tr>
<tr>
<td>19/63</td>
<td>0.76 (0.48-1.26)</td>
</tr>
<tr>
<td>311/544</td>
<td>1.22 (0.99-1.49)</td>
</tr>
<tr>
<td>743/1,483</td>
<td>0.96 (0.80-1.15)</td>
</tr>
<tr>
<td>530/1,044</td>
<td>1.02 (0.85-1.24)</td>
</tr>
<tr>
<td>330/588</td>
<td>1.33 (1.09-1.63)</td>
</tr>
</tbody>
</table>

- ■ BMI 18.5-24.9
- ● BMI 25.0-29.9
- ● BMI 30.0-34.9
- ▲ BMI ≥35.0
Figure 2E. Using a Stricter Metabolic Health Definition (n=4,551)

<table>
<thead>
<tr>
<th>Event/n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21/56</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>18/50</td>
<td>0.73 (0.39-1.38)</td>
</tr>
<tr>
<td>7/26</td>
<td>0.68 (0.29-1.61)</td>
</tr>
<tr>
<td>1/4</td>
<td>0.61 (0.08-4.53)</td>
</tr>
<tr>
<td>426/776</td>
<td>1.29 (0.83-2.01)</td>
</tr>
<tr>
<td>902/1,816</td>
<td>1.06 (0.69-1.64)</td>
</tr>
<tr>
<td>571/1,176</td>
<td>1.08 (0.70-1.68)</td>
</tr>
<tr>
<td>348/647</td>
<td>1.44 (0.92-2.24)</td>
</tr>
</tbody>
</table>

Metabolically Healthy

Metabolically Unhealthy

Figure 2F. Metabolically Healthy, Excluding Those with Updated Unhealthy Status (n=461)

<table>
<thead>
<tr>
<th>Event/n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>76/168</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>73/188</td>
<td>0.82 (0.58-1.15)</td>
</tr>
<tr>
<td>19/75</td>
<td>0.45 (0.27-0.76)</td>
</tr>
<tr>
<td>6/30</td>
<td>0.56 (0.24-1.31)</td>
</tr>
</tbody>
</table>

Metabolically Healthy

BMI 18.5-24.9  • BMI 25.0-29.9  • BMI 30.0-34.9  ▲ BMI ≥35.0
a HR denotes hazard ratio and 95% CI denotes 95% confidence interval. Metabolically healthy represents having ≤ 1 metabolic components as defined by a modified ATP III criteria, except for panel D and E. Panel A shows results for the total study population, metabolically healthy, and metabolically unhealthy. Panel B shows the results for never-smokers with no identified chronic disease burden, defined as having none of the ICD-9 codes (excluding the ICD-9 code for diabetes-250.XX) that comprise the Charlson Index. Panel C shows the results for never-smokers, with the exclusion of deaths occurring in the first 5 years of follow-up. Panel D shows the results using a modified metabolic health definition - metabolically healthy represents having ≤ 1 metabolic components as defined by a modified ATP III criteria and not having diabetes. Panel E shows the results using a stricter metabolic health definition - metabolically healthy represents having 0 metabolic components as defined by a modified ATP III criteria. Panel F shows the results among metabolically healthy, excluding those who became metabolically unhealthy during follow-up (Of 921 metabolically healthy participants at baseline, 103 did not have updated metabolic status and 357 became metabolically unhealthy, resulting in 461 for this sensitivity analysis). All estimates are adjusted for age, sex, smoking status (never, former, or smoker) (in Panels A, D, E, and F), alcohol drinker (yes or no), LDL cholesterol (mg/dL), hypercholesterolemia drug (yes or no), and disease burden (0, 1, 2, or ≥ 3 diseases) (in Panels A, C, D, E, and F).
**SUPPLEMENTARY MATERIAL**

**Table 4.4 (Supplementary Table 1) All-cause Mortality in Relation to Body Mass Index and Individual Metabolic Components (n=4,551)**

<table>
<thead>
<tr>
<th>Body Mass Index (kg/m²)</th>
<th>18.5-24.9</th>
<th>25.0-29.9</th>
<th>30.0-34.9</th>
<th>≥35.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolically Healthy(^a)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Triglycerides Reference</td>
<td>1.22</td>
<td>(1.01-1.47)</td>
<td>0.87</td>
<td>(0.74-1.02)</td>
</tr>
<tr>
<td>High-density lipoprotein Reference</td>
<td>1.15</td>
<td>(0.93-1.43)</td>
<td>0.82</td>
<td>(0.72-0.94)</td>
</tr>
<tr>
<td>Blood Pressure Reference</td>
<td>1.10</td>
<td>(0.83-1.46)</td>
<td>0.91</td>
<td>(0.65-1.27)</td>
</tr>
<tr>
<td>Blood Glucose or Diabetes Reference</td>
<td>1.21</td>
<td>(1.00-1.45)</td>
<td>0.85</td>
<td>(0.72-1.00)</td>
</tr>
</tbody>
</table>

\(^a\) Metabolically healthy represents triglycerides <1.69 mmol/L (<150 mg/dL), HDL ≥1.03 mmol/L (≥40 mg/dL) – men or ≥1.29 mmol/L (≥50 mg/dL) – women, blood pressure <130/<85 mm Hg or no diagnosis of hypertension, or glucose <5.56 mmol/L (<100 mg/dL) or no diagnosis of diabetes. HR denotes hazard ratio and 95% CI denotes 95% confidence interval. Model is adjusted for age, sex, smoking status (never, former, or smoker), alcohol drinker (yes or no), low-density lipoprotein cholesterol, hypercholesterolemia drug (yes or no), and disease burden (0, 1, 2, or ≥ 3 diseases).
Table 4.5 (Supplementary Table 2) All-cause Mortality in Relation to Body Mass Index and Metabolic Status - Propensity Score Weights (n=4,551)

<table>
<thead>
<tr>
<th>Body Mass Index (kg/m²)</th>
<th>18.5-24.9</th>
<th>25.0-29.9</th>
<th>30.0-34.9</th>
<th>≥35.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolically Healthy⁴</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Event/n</td>
<td>139/293</td>
<td>308/539</td>
<td>187/401</td>
<td>733/1,465</td>
</tr>
<tr>
<td>HRs (95% CIs)</td>
<td>Reference</td>
<td>1.25</td>
<td>0.97</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>(1.00-1.56)</td>
<td>(0.77-1.23)</td>
<td>(0.80-1.18)</td>
<td>(0.41-0.84)</td>
</tr>
</tbody>
</table>

⁴ Metabolically healthy represents having ≤ 1 metabolic components as defined by a modified ATP III criteria. HR denotes hazard ratio and 95% CI denotes 95% confidence interval. Propensity score weights were estimated by generalized boosted models.
### Table 4.6 (Supplementary Table 3) All-cause Mortality in Relation to Body Mass Index and Metabolic Status – Excluding Those on Cholesterol Lowering Medicine (n=2,011)

<table>
<thead>
<tr>
<th>Body Mass Index (kg/m²)</th>
<th>18.5-24.9</th>
<th>25.0-29.9</th>
<th>30.0-34.9</th>
<th>≥35.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolically Healthy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>HRs (95% CIs)</td>
<td>Reference</td>
<td>1.34</td>
<td>0.83</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>(1.03-1.75)</td>
<td>(0.62-1.11)</td>
<td>(0.73-1.18)</td>
<td>(0.37-0.90)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Metabolically healthy represents having ≤ 1 metabolic components as defined by a modified ATP III criteria. HR denotes hazard ratio and 95% CI denotes 95% confidence interval. Model is adjusted for age, sex, smoking status (never, former, or smoker), alcohol drinker (yes or no), LDL cholesterol, and disease burden (0, 1, 2, or ≥ 3 diseases).
Table 4.7 (Supplementary Table 4) All-cause Mortality in Relation to Body Mass Index and Metabolic Status – Excluding Those without Diabetes Diagnosis but On Diabetics Medications (n=4,550)

<table>
<thead>
<tr>
<th>Body Mass Index (kg/m²)</th>
<th>18.5-24.9</th>
<th>25.0-29.9</th>
<th>30.0-34.9</th>
<th>≥35.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolically Healthy(^a)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Event/n</td>
<td>139/293</td>
<td>308/539</td>
<td>187/401</td>
<td>733/1,465</td>
</tr>
<tr>
<td>HRs (95% CIs)</td>
<td>Reference</td>
<td>1.24</td>
<td>0.90</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>(1.01-1.52)</td>
<td>(0.73-1.13)</td>
<td>(0.80-1.16)</td>
<td>(0.42-0.80)</td>
</tr>
</tbody>
</table>

\(^a\) Metabolically healthy represents having ≤ 1 metabolic components as defined by a modified ATP III criteria. HR denotes hazard ratio and 95% CI denotes 95% confidence interval. Model is adjusted for age, sex, smoking status (never, former, or smoker), alcohol drinker (yes or no), LDL cholesterol, hypercholesterolemia drug (yes or no), and disease burden (0, 1, 2, or ≥ 3 diseases).
Table 4.8 (Supplementary Table 5) All-cause Mortality in Relation to Body Mass Index and Metabolic Status – Excluding Those without Hypertension Diagnosis but On Blood Pressure Medications (n=4,369)

<table>
<thead>
<tr>
<th>Body Mass Index (kg/m²)</th>
<th>18.5-24.9</th>
<th>25.0-29.9</th>
<th>30.0-34.9</th>
<th>≥35.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolically Healthy*</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Event/n</td>
<td>121/264</td>
<td>302/530</td>
<td>160/351</td>
<td>712/1,429</td>
</tr>
<tr>
<td>HRs (95% CIs)</td>
<td>Reference</td>
<td>1.25</td>
<td>0.90</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>(1.01-1.54)</td>
<td>(0.71-1.14)</td>
<td>(0.80-1.18)</td>
<td>(0.38-0.76)</td>
</tr>
</tbody>
</table>

* Metabolically healthy represents having ≤ 1 metabolic components as defined by a modified ATP III criteria. HR denotes hazard ratio and 95% CI denotes 95% confidence interval. Model is adjusted for age, sex, smoking status (never, former, or smoker), alcohol drinker (yes or no), LDL cholesterol, hypercholesterolemia drug (yes or no), and disease burden (0, 1, 2, or ≥ 3 diseases).
Chapter 5

OBESITY AS A RISK FACTOR FOR DEVELOPING FUNCTIONAL LIMITATION AMONG OLDER ADULTS: RESULTS FROM CONDITIONAL INFERENCE TREE ANALYSIS
ABSTRACT

Background: Previous studies have examined the association between body mass index (BMI) and functional decline using traditional regression approaches. Yet, a data mining approach may provide different interpretive options, especially for risk classification questions with complex interactions.

Objective: To use conditional inference tree analysis – a data mining approach – to construct a risk stratification algorithm for risk of developing functional limitation, based on BMI and other potential risk factors (e.g., age, sex, and health/lifestyle factors) among Geisinger Rural Aging Study (GRAS) participants who reported no functional limitations at baseline.

Methods: We included 1,951 GRAS participants, aged 73.1±4.2 (mean±SD) years, who had no functional limitations (i.e., who reported not having any limitations of activities of daily living or instrumental activities of daily Living) at baseline. In addition to conditional inference tree analysis, we analyzed the data with multivariate stepwise logistic regression and compared the two approaches (e.g., cross-validation).

Results: Over a mean of 9.2±1.7 years of follow up, 221 individuals developed functional limitation. Individuals were stratified into four risk groups via conditional inference tree analysis based on three significant risk factors (higher BMI, age, and comorbidity). Compared to the low risk group, all other groups had significantly higher risk of developing functional limitation. The odds ratio comparing two extreme categories was 9.09 (95% confidence interval: 4.68, 17.6).

Conclusions: Higher BMI, age, and comorbidity were consistently identified as significant risk factors for functional decline among older individuals across all
approaches and analyses. Our study demonstrated the potential benefits of using a data mining approach in addition to traditional regression methods to address health and clinical questions, which may enhance the translation of findings into practice.
INTRODUCTION

A number of studies have reported a strong association between body mass index (BMI) and functional decline among older persons using traditional regression approaches. However, regression limits one’s ability to address risk classification questions with complex interactions (1). Furthermore, traditional regression approaches are limited in their ability to translate results for meaningful clinical application (e.g., clinicians usually identify patients as high or low risk in contrast to the risk ratio as determined by regression methods) (1,2). Thus, we sought to use conditional inference tree analysis - a data mining approach, which is a non-parametric yet powerful statistical method that is effective in addressing those issues. The conditional inference tree analysis is a tree-structured regression model that uses an unbiased recursive partitioning technique (3,4). It provides a tree-based data visualization of the sophisticated interactions among variables with regard to the outcome, which could potentially enhance translatability of findings into practice (1). As noted in previous literature, “this process of reconciling the clinical and statistical relevance of variables in the data ultimately yields a more well informed and statistically informative model than either a singularly clinical or statistical approach.” (2)

Therefore, we used conditional inference tree analysis to construct a risk stratification algorithm for risk of developing functional decline, based on BMI and other potential risk factors (e.g., age, sex, lifestyle factors, and disease burden) in a prospective study including 1,951 older adults who reported no functional limitations at baseline.
METHODS

Study Population

The Geisinger Rural Aging Study (GRAS) is comprised of a cohort of northeastern and central Pennsylvanians ≥ 65 years of age who were enrolled in a Medicare-managed risk program offered through the Geisinger Health System (Danville, PA) (5). There were 4,565 GRAS participants that received primary care services at the Geisinger Medical Center (Danville, PA) and were active in the electronic medical record (EMR) Epic Systems (Verona, WI) between January 1, 2001 and December 31, 2004.

Between 1999 and 2003, we mailed a questionnaire to assess baseline functional status (i.e., activities of daily living (ADL) and instrumental activities of daily living (IADL)) (6,7) to all GRAS participants. The questionnaire was completed by 3,583 GRAS participants (78.5%). In this prospective analysis, we excluded those (n=261) who had baseline functional limitation (i.e., who indicated having any of the ADLs or IADLs). Between 2009 and 2011, we mailed the same questionnaire for follow up. Of the remaining 3,322 participants, 773 died and 598 did not return the questionnaire, leaving 1,951 individuals for the final analysis (Figure 5.1).

Compared to participants who were excluded from the study because of incomplete baseline or follow-up questionnaires, those who were included were slightly younger (mean 73.1 vs. 73.9 years), healthier (as suggested by a lower mean modified Charlson Index 1.1 vs. 1.4) and had lower BMI (mean 29.3 vs. 29.8 kg/m²), but similar sex proportion (men: 38.1 vs. 39.6%).
The study protocol was approved by the Institutional Review Board at the Geisinger Health System and an IRB-approved Data Sharing Agreement was in place with the Pennsylvania State University.

**Assessment of functional limitation**

We assessed functional status using the ADL and IADL questions “I usually or always need assistance with (check all that apply): bathing, dressing, grooming, toileting, eating, walking or moving about, traveling (outside the home), preparing food, and shopping for food or other necessities.”(6,7) at baseline and again in 2009-2011. Functional limitation (yes or no) was defined as reporting any of the nine items.

**Assessment of predictors**

We extracted information for all potential predictors from the EMR and used the earliest plausible values between January 1, 2001 and December 31, 2004 as baseline. These variables included weight, height, age, sex, smoking status (never/former/current smoker), alcohol drinker (yes/no), blood glucose, systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, hypercholesterolemia medication (yes/no), hypertension medication (yes/no), diabetic medication (yes/no), and International Classification of Diseases (ICD)-9) codes. Strict algorithms were implemented to detect for inaccurate and implausible values before selecting the earliest plausible measurements from the baseline period. Briefly, we first excluded implausible weights (<24.9 kilograms (kg) [<55 pounds] or >453.6 kg [>1,000 pounds]) and heights (<111.8 centimeters (cm) [<44 inches] or >228.6 cm [>90 inches]) and then further identified inaccurate measurements by comparing all available values for each individual person using pre-
established criteria (8). As a result, approximately 0.23% and 2.39% of the weights and heights, respectively, were excluded. We also eliminated implausible laboratory and blood pressure measurements: blood glucose <30 or >600 mg/dL (<1.67 or >33.3 mmol/L), triglyceride <10 or >2000 mg/dL (<0.11 or >22.60 mmol/L), HDL cholesterol <10 or >120 mg/dL (<0.26 or >3.10 mmol/L), LDL cholesterol <30 or >300 mg/dL (<0.78 or >7.76 mmol/L), SBP <60 or >250 mmHg, DBP <40 or >140 mmHg (8–12).

BMI (kg/m²) was calculated using weights and heights measured by trained health professionals according to standard outpatient clinic visit protocol (e.g., without over-garments and shoes). The definition of metabolic health status was based on a modified Adult Treatment Panel III guideline similar to that utilized by Wildman and colleagues (13,14). Metabolically healthy represented having ≤1 of the following conditions: fasting glucose ≥100 mg/dL (≥5.56 mmol/L) or diabetes diagnosis (ICD-9 250.XX); blood pressure ≥130/85 mm Hg or hypertension diagnosis (ICD-9 401.XX-405.XX); triglycerides ≥150 mg/dL (≥1.69 mmol/L); and high density lipoprotein (HDL) cholesterol for women <50 mg/dL (<1.29 mmol/L) or for men <40 mg/dL (<1.03 mmol/L). We did not include lipid ICD-9 codes as part of the definition because the ICD-9 code for hypertriglyceridemia was not commonly used and there was no ICD-9 code for low HDL cholesterol. Waist circumference was not available. The modified Charlson Index was calculated using ICD-9 codes (excluded ICD-9 code for diabetes - 250.XX) with appropriate weights (15). We excluded ICD-9 codes for diabetes as they were already being considered as a metabolic health status variable. We also did not include the “age” component because we treated it as an independent variable in the models.
Statistical Analyses

We used conditional inference tree analysis to construct a risk stratification algorithm for developing functional limitation with 11 potential predictors (i.e., BMI, age, sex, smoking status (never/former/current smoker), alcohol drinker (yes/no), metabolically healthy (yes/no), LDL, hypercholesterolemia medication (yes/no), hypertension medication (yes/no), diabetic medication (yes/no), and the modified Charlson Index). Briefly, conditional inference tree analysis generates a decision tree by recursively partitioning the population of interest into sub-populations based on univariate splits (3,4). The following two steps are performed repeatedly:

1. The algorithm first examines whether there is a statistically significant association between the outcome and any predictor. If not, it stops without further generating subgroups. Since multiple predictors are considered, the Bonferroni correction is used to counteract the problem of multiple comparisons. If yes, it selects the predictor with the highest explanatory ability (i.e., lowest $P$ value), and move to Step 2.

2. For the predictor chosen in Step 1, the algorithm finds the split that best separates the population among all potential binary splits such that the resulting two sub-populations are as different from each other as possible (i.e., by comparing $\chi^2$ statistic for binary outcome).

We generated a risk stratification model by calculating the percentage of individuals who developed functional limitation within each terminal node. We then examined the odds ratios (ORs) and associated 95% confidence intervals (CIs) among
risk groups, and evaluated the prediction accuracy using the area under receiver operating characteristic curve (AUC).

For comparison purpose, we performed a multivariate stepwise logistic regression with the same set of predictors except that BMI was treated as a categorical variable as there may be a nonlinear association between BMI and functional limitation (16). BMI was classified per the National Institutes of Health guidelines: underweight (<18.5), desirable (18.5-24.9), overweight (25.0-29.9), obesity class I (30.0-34.9), and obesity class II/III (≥35.0) (17). Variables with $P < 0.15$ were allowed to enter into the model but only those with $P < 0.05$ were permitted to remain in the final model. We elected to use the same significance level that was required for a binary split in the conditional inference tree analysis to enhance comparability (3,18), and the same set of cross-validations for prediction accuracy evaluation.

We performed three sensitivity analyses. First, we compared the average AUC over 5 validation datasets between conditional inference tree analysis and the traditional logistic regression model. A similar approach has been used previously (19). Second, individuals with less favorable baseline characteristics may be more likely to die or not to complete the follow-up questionnaire. To address this concern, we used multiple imputation based on a propensity score approach that was previously described (20). We first constructed a propensity model by using the logistic regression method to estimate the probability of developing functional limitation with existing predictors among those who were included in the study. Propensity scores are then applied to those with missing functional limitation data according to their baseline characteristics. Individuals with high propensity scores would be considered as “had developed functional limitation”. We
generated five complete datasets and consequently created five conditional inference
trees to examine variables that were included in each tree model. Lastly, we constructed a
c conditional inference tree excluding those with any amputation (n=25) as it could affect
functional limitation regardless of baseline characteristics.

P-value <0.05 (two-tailed) was considered significance. Statistical analyses were
performed using SAS 9.4 (SAS Institute; Cary, NC) and the conditional inference trees
were constructed in the R environment 3.1.1 (https://cran.r-
project.org/web/packages/party/index.html) (18).
RESULTS

Of the 1,951 GRAS participants (99.8% Caucasian; 61.9 % women; mean age 73.1 years [Range, 66.9 to 90.4 years]; mean BMI 29.3 kg/m² [Range, 16.6 to 52.6 kg/m²]) who were included in the final analysis, 221 individuals developed functional limitation over a mean of 9.2 years (range, 6.7 to 12.1 years) of follow up. In general, those who developed functional limitation were older, more likely to have diabetes and be on hypertension and diabetes medications, and had higher BMI, blood glucose level, and modified Charlson Index at the baseline (Table 5.1). They were also less likely to report drinking alcohol.

Of the 11 predictors that were examined, the conditional inference tree analysis identified age (splitting value at 75.7 years), modified Charlson Index (splitting value at 0), and BMI (splitting value at 38.5) as significant risk factors that could discriminate between those who developed functional limitation and those who did not (Figure 5.2). Based on these factors, individuals were stratified into four risk groups: 1) low risk: age ≤75.7 and modified Charlson Index = 0 (6.4% of participants developed functional limitation); 2) intermediate risk I: age ≤75.7, modified Charlson Index >0, and BMI ≤38.5 (10.2% functional limitation); 3) intermediate risk II: age >75.7 (17.7% functional limitation); and 4) high risk: age ≤75.7, modified Charlson Index >0, and BMI >38.5 (38.3% functional limitation). Compared to the low risk group, all other groups had significantly higher risk of developing functional limitation (Figure 5.3).

Multivariate stepwise logistic regression identified age, BMI, reporting alcohol consumption, hypertension medication, and modified Charlson Index as significant risk factors for developing functional limitation:
\[
\text{log odds of developing any functional limitation} = 0.08 \times \text{age} - 8.95 \times \\
\text{underweight} + 1.93 \times \text{overweight} + 2.07 \times \text{obese class I} + 2.95 \times \text{obese class II/III} - 0.18 \times \text{alcohol drinker} + 0.26 \times \text{hypertension medication} + 0.15 \times \text{modified Charlson Index} - 10.6.
\]

The AUCs for conditional inference tree analysis and the logistic regression model were similar (0.64 vs 0.67), which was consistently shown in the 5-fold cross-validation study (Supplementary Table 1 (Table 5.2)). Similarly, BMI, age, and modified Charlson (except for one training set) were consistently identified as significant variables in all models (Supplementary Table 2 (Table 5.3)).

The conditional inference trees that were generated from cohorts based on the propensity score approach also identified age, modified Charlson Index, and BMI as significant risk factors for developing functional limitation (Supplementary Table 3 (Table 5.4)). In general, individuals in the lowest risk group had lower BMI and modified Charlson Index, and were younger, while only higher BMI was consistently recognized as a characteristic of the highest risk group (Supplementary Table 4 (Table 5.5)). Lastly, exclusion of those with amputation produced the same conditional inference tree (data not shown).
DISCUSSION

In our study, elevated BMI was consistently identified as a significant risk factor for developing future functional limitation across all approaches and analyses, including conditional inference tree analysis, logistic regression modeling, and also sensitivity analyses. This is consistent with previous studies based on conventional approaches (e.g., logistic regression), which reported an association between elevated BMI and higher risk for developing functional limitation among older persons (16,21–26). For example, the Established Populations for Epidemiologic Studies of the Elderly reported that BMI ≥30 was significantly associated with greater risk of developing ADL disability among 12,725 adults aged ≥65 years over a 7-year follow-up period (21). In the Medicare Current Beneficiary Survey Study of 20,975 older adults aged ≥65 years, higher BMI was associated with new or exacerbated ADL or IADL disability in a dose-response manner over a two-year period (22).

This study demonstrated the potential benefits of using a data mining approach (e.g., conditional inference tree analysis) in addition to traditional regression methods to better address risk classification questions. The conditional inference tree analysis generated a reliable risk stratification algorithm for developing functional limitation based upon health and laboratory data that were available in the EMR. The overall percentage of people developing functional limitation for our cohort was 11.3% but this percentage differed by almost 6-fold (from low risk group: 6.40% to high risk group: 38.30%) based on age, modified Charlson Index, and BMI. Furthermore, our findings highlight the strength of conditional inference tree analysis in modeling complex interactions. Traditional regression methods can provide researchers with an idea of how
a predictor associates with an outcome while controlling for other covariates, but it is difficult to utilize such findings to generate a clinical decision rule. Our conditional inference tree analysis suggests that for an individual ≤75.7 years with a modified Charlson Index >0, the addition of having a BMI >38.5 can place that individual in a higher risk group (i.e., high risk group vs. intermediate risk I group) for functional decline. Knowing this information could assist clinicians in identifying at-risk individuals and allocating healthcare resources. It is important to note that conditional inference tree analysis (and data mining approaches in general) also requires adequate sample size to reach the threshold for appropriate binary splits in the tree structure similar to traditional regression methods when there is a lack of power to detect for significant results (i.e., wide 95% confidence interval) (1,19).

Age and comorbidity have long been recognized as risk factors for functional limitation (23,25,27). The fact that BMI, in addition to age and comorbidity, was identified as a significant predictor further confirms its added value in the context of predicting future functional decline. Previous literature has also reported BMI as an independent risk factor for functional limitation (16,21–26). Excess body weight is associated with greater risk of several conditions that afflict older persons, such as osteoarthritis of the knees and reduced muscle strength (i.e., in those with sarcopenic obesity), which may negatively impact functional ability (27–32).

In our analysis, among adults aged ≤ 75.7 years the algorithm further stratified individuals into risk groups based upon modified Charlson Index and BMI, but not among participants aged >75.7 years. This may be due to small sample size in this older population as 44.6% of the “older” participants had died between baseline and follow-up,
compared to only 21.2% among individuals aged ≤75.7 years. In fact, when we used the same stratification rule identified in the “younger” participants with individuals older than 75.7 years, the percentages of those who developed functional limitation in each of the three risk groups (low risk: Charlson Index = 0, intermediate risk: modified Charlson Index >0 + BMI ≤38, and high risk: modified Charlson Index >0 + BMI >38) were 17.7% (31/175), 17.3% (49/283), and 33.3% (2/6), respectively. Our speculation was further confirmed by the findings from the propensity score models, which showed the added value of BMI even among the individuals aged >75.7 years (data not shown).

Several limitations should be noted. First, we relied on self-reported ADLs and IADLs, although those measures have been shown to correlate well with more objective physical performance tests (33–35). Second, we did not have any physical activity information. Physical activity is related to functional limitation, independent of BMI, age, sex, disease status, and other sociodemographic and psychosocial factors (25). Third, body composition data were not available. Fat and muscle mass measurements, along with waist circumference, have been shown to be significant predictors of functional limitation (26,36,37). Sarcopenic obesity is associated with greater risk of functional decline (32,38,39). Future studies are warranted to explore whether including body composition data would allow for a more precise risk stratification of individuals in relation to functional limitation. Moreover, we did not have detailed information (i.e., how often and amount) on alcohol consumption. Our findings from the stepwise logistic regression model showed that those who drank alcohol were less likely to have functional decline. Previous studies (16,40) have reported a U-shaped association between alcohol intake and functional decline, with the lowest risk among moderate drinkers. One study
observed a substantial attenuation of this relationship with the adjustment of lifestyle-related factors. Thus, we speculate that the “alcohol” variable in our cohort may be a proxy for more favorable behavioral and lifestyle factors that could benefit functional ability. However, the anti-inflammatory effect of alcohol could also be another potential explanation. Although we were mainly interested in examining the associations between risk factors, specifically BMI, and functional decline among survivors, we constructed 5 propensity score models to impute functional limitation data for those who had died or did not complete the follow-up survey. Results remained consistent. Lastly, our results may not be generalizable to other populations because members of our cohort were 99.8% Caucasians who resided in northeastern and central Pennsylvania. However, our results are comparable to those reported by other studies with more diverse populations.

CONCLUSIONS

In conclusion, higher BMI, age, and comorbid disease, were consistently identified as significant risk factors for functional decline among older individuals across all approaches and analyses. Our study demonstrated the potential benefits of using a data mining approach in addition to traditional regression methods to address health and clinical questions, which may enhance the translation of findings into practice.
REFERENCES

1. Lewis RJ. An introduction to classification and regression tree (CART) analysis [Internet]. Available from: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.95.4103&rep=rep1&type=pdf


**Table 5.1** Baseline Characteristics of the Study Population, by Functional Limitation Status (n=1,951)*

<table>
<thead>
<tr>
<th>Develop Any Functional Limitation</th>
<th>No (n=1,730)</th>
<th>Yes (n=221)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>29.1 (0.1)</td>
<td>30.8 (0.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>72.9 (0.1)</td>
<td>74.4 (0.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Men, %</td>
<td>38.7</td>
<td>33.4</td>
<td>0.13</td>
</tr>
<tr>
<td>Smoking Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never, %</td>
<td>56.7</td>
<td>59.1</td>
<td>0.46</td>
</tr>
<tr>
<td>Former, %</td>
<td>34.0</td>
<td>31.0</td>
<td>0.32</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>9.2</td>
<td>9.9</td>
<td>0.75</td>
</tr>
<tr>
<td>Alcohol Drinker, %</td>
<td>34.9</td>
<td>27.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Metabolically Unhealthy, %</td>
<td>76.0</td>
<td>78.4</td>
<td>0.42</td>
</tr>
<tr>
<td>Blood Glucose (mg/dL)*</td>
<td>108.4 (0.7)</td>
<td>112.9 (2.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>24.6</td>
<td>30.5</td>
<td>0.05</td>
</tr>
<tr>
<td>Systolic (mmHg)</td>
<td>139.1 (0.4)</td>
<td>137.1 (1.2)</td>
<td>0.12</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>76.9 (0.2)</td>
<td>76.3 (0.7)</td>
<td>0.38</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>75.2</td>
<td>78.5</td>
<td>0.29</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)*</td>
<td>173.6 (2.4)</td>
<td>179.0 (6.6)</td>
<td>0.44</td>
</tr>
<tr>
<td>HDL Cholesterol (mg/dL)*</td>
<td>51.5 (0.34)</td>
<td>51.1 (1.0)</td>
<td>0.67</td>
</tr>
<tr>
<td>LDL Cholesterol (mg/dL)*</td>
<td>117.6 (0.8)</td>
<td>114.4 (2.3)</td>
<td>0.19</td>
</tr>
<tr>
<td>Medications for:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypcholesteremia, %</td>
<td>56.2</td>
<td>59.7</td>
<td>0.33</td>
</tr>
<tr>
<td>Condition</td>
<td>Value 1</td>
<td>Value 2</td>
<td>p-value</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>81.9</td>
<td>90.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>18.4</td>
<td>24.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Modified Charlson Index</td>
<td>1.1 (0.0)</td>
<td>1.4 (0.1)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; mg/dL, milligrams per deciliter; mmHg, millimeter of mercury.

* Age- and sex-adjusted means (standard errors) for continuous variables and percentages for categorical variables.

b Metabolically healthy represents having ≤ 1 metabolic components as defined by a modified ATP III criteria.

c To convert the values for blood glucose to millimoles per liter (mmol/L), multiply by 0.05556. To convert the values for triglycerides to mmol/L, multiply by 0.01129. To convert HDL and LDL cholesterol to mmol/L, multiply by 0.02586.
Figure 5.1 Flow Chart of Study Geisinger Rural Aging Study (GRAS) Participants

GRAS participants who had primary care services at the Geisinger Medical Center and were active in the electronic medical record between January 1, 2001 and December 31, 2004 (n = 4,565)

Exclusion (n = 982)
- Did not complete baseline questionnaire (n = 974)
- Died (n = 8)

Had complete baseline (1999-2003) activities of daily living (ADL) and instrumental activities of daily living (IADL) data (n=3,583)

Exclusion (n = 261)
- Had baseline functional limitation (i.e., indicated having any of the ADL or IADL item)

Had no baseline (1999-2003) functional limitation (n=3,322)

Exclusion (n = 1,371)
- Did not complete follow-up questionnaire (n = 598)
- Died (n = 773)

Had complete follow-up (2009-2011) activities of daily living (ADL) and instrumental activities of daily living (IADL) data in 1999-2003 (n=1,951)
Figure 5.2 Predictors of Developing Any Functional Limitation and Risk Stratification (n=1,951)\textsuperscript{a}

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{figure52.png}
\end{figure}

\textsuperscript{a} Individuals were stratified into four risk groups: 1) low risk: age \( \leq 75.7 \) and modified Charlson Index = 0 (6.4% of participants developed functional limitation); 2) intermediate risk I: age \( \leq 75.7 \), modified Charlson Index >0, and BMI \( \leq 38.5 \) (10.2% functional limitation); 3) intermediate risk II: age >75.7 (17.7% functional limitation); and 4) high risk: age \( \leq 75.7 \), modified Charlson Index >0, and BMI >38.5 (38.3% functional limitation).
Figure 5.3 Odds Ratios of Developing Any Functional Limitation Between Risk Groups
Identified by Conditional Inference Tree Analysis (n=1,951)

<table>
<thead>
<tr>
<th>Event/n</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>44/688</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>77/752</td>
<td>1.67 (1.14-2.46)</td>
</tr>
<tr>
<td>82/464</td>
<td>3.14 (2.13-4.63)</td>
</tr>
<tr>
<td>18/47</td>
<td>9.09 (4.68-17.62)</td>
</tr>
</tbody>
</table>

- ■ Low Risk
- ♦ Intermediate Risk I
- ● Intermediate Risk II
- ▲ High Risk
**SUPPLEMENTARY MATERIAL**

**Table 5.2 (Supplementary Table 1) 5-Fold Cross-Validation: Area Under Receiver Operating Characteristic Curve (AUC) of Conditional Inference Tree Analysis and Logistic Regression Model**

<table>
<thead>
<tr>
<th>Set #</th>
<th>Conditional Inference Tree</th>
<th>Logistic Regression</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Training</td>
<td>Validation</td>
</tr>
<tr>
<td>1</td>
<td>0.66</td>
<td>0.61</td>
</tr>
<tr>
<td>2</td>
<td>0.62</td>
<td>0.61</td>
</tr>
<tr>
<td>3</td>
<td>0.63</td>
<td>0.59</td>
</tr>
<tr>
<td>4</td>
<td>0.63</td>
<td>0.54</td>
</tr>
<tr>
<td>5</td>
<td>0.63</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td><strong>0.63</strong></td>
<td><strong>0.60</strong></td>
</tr>
</tbody>
</table>

**AUCs**
Table 5.3 (Supplementary Table 2) 5-Fold Cross-Validation: Significant Predictors
Identified by Conditional Inference Tree Analysis

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</thead>
<tbody>
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<td></td>
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<tr>
<td>BMI</td>
<td>X</td>
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<tr>
<td>Age</td>
<td>X</td>
</tr>
<tr>
<td>Modified Charlson Index</td>
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Table 5.4 (Supplementary Table 3) Propensity Score Models: Significant Predictors

Identified by Conditional Inference Tree Analysis

<table>
<thead>
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<th>Propensity Score Model</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Age</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Modified Charlson Index</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes Medication</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
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</tr>
<tr>
<td>Male Sex</td>
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<td>X</td>
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<tr>
<td>Alcohol Drinker</td>
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<td></td>
<td></td>
<td>X</td>
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</tbody>
</table>
Table 5.5 (Supplementary Table 4) Propensity Score Models: Baseline Characteristics of the Lowest and Highest Risk Stratification Groups

<table>
<thead>
<tr>
<th>Propensity Score Model #</th>
<th>Lowest Risk Group</th>
<th>Highest Risk Group</th>
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<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>BMI</td>
<td>≤37.79</td>
<td>≤35.58</td>
</tr>
<tr>
<td>Age</td>
<td>≤76.64</td>
<td>≤71.92</td>
</tr>
<tr>
<td>Modified Charlson Index</td>
<td>≤2</td>
<td>≤0</td>
</tr>
<tr>
<td>Hypertension Medication</td>
<td>Yes</td>
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<tr>
<td>Diabetes Medication</td>
<td>No</td>
<td></td>
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<tr>
<td>Alcohol Drinker</td>
<td>No</td>
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Chapter 6

WEIGHT CHANGE AND ALL-CAUSE MORTALITY IN OLDER ADULTS:
A META-ANALYSIS

A reprint is contained in the following pages.

This is an Accepted Manuscript of an article published in the Journal of Nutrition in Gerontology and Geriatrics online [November 16, 2015], available online:

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Weight Change and All-Cause Mortality in Older Adults: A Meta-Analysis

Feon W. Cheng MPH, RD, CHTS-CP, Xiang Gao MD, PhD & Gordon L. Jensen MD, PhD

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Review

Weight Change and All-Cause Mortality in Older Adults: A Meta-Analysis

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This meta-analysis of observational cohort studies examined the association between weight change (weight loss, weight gain, and weight fluctuation) and all-cause mortality among older adults. We used Pub Med (MEDLINE), Web of Science, and Cochrane Library to identify prospective studies published in English from inception to November 2014. Seventeen prospective studies met the inclusion criteria and were included in this meta-analysis. Higher all-cause mortality risks were noted with weight change: weight loss (pooled RR, 1.67; 95% CI, 1.51–1.85; p < 0.001 for heterogeneity), weight gain (pooled RR, 1.21; 95% CI, 1.09–1.33; p = 0.03 for heterogeneity), and weight fluctuation (pooled RR, 1.53; 95% CI, 1.36–1.72; p = 0.43 for heterogeneity). Similar results were observed with stricter criteria for sensitivity analyses. None of the study characteristics had statistically significant effects on the pooled RR, except for study quality on weight loss. Weight change is associated with higher mortality risk among community-dwelling adults 60 years and older.

KEYWORDS elderly, meta-analysis, mortality, obesity, weight change

INTRODUCTION

Older adults are among the fastest growing segments in the US population (1). The number of older persons is projected to double by 2030, corresponding to

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approximately 71 million individuals and comprising nearly 20% of the US population (2, 3). Overweight or obesity now afflict about 71% of older persons (4–6). While the associated mortality risk with excess body weight is well documented in the younger population, an “obesity paradox” with reduced mortality has been described for overweight older adults (7).

Observational studies have reported higher risk of mortality with weight change among both middle-aged and older adults (8–10). Previous reviews of weight change and all-cause mortality have mainly focused on weight loss and not weight gain (11–13). Furthermore, most of them included both middle-aged and older adults in the same analysis, making it difficult to differentiate the effects of age in this relationship (11–14). Because body composition, weight change pattern, and relationship between body weight and mortality appear to vary by age, it is important to further investigate whether weight change associations with mortality persist in the aging population (15–17). Better understanding of the impact of weight change on longevity is crucial from both public health and clinical standpoints. Thus, we conducted a meta-analysis of observational cohort studies to examine current literature on the association between weight change (weight loss, weight gain, and weight fluctuation) and all-cause mortality among older adults.

**METHODS**

This meta-analysis followed the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guideline for study selection, data extraction, meta-analyses, and results reporting (18).

**Search Strategy**

An electronic literature search of the three full databases—Pub Med (MEDLINE) database of the United States National Library of Medicine, Web of Science, and Cochrane Library—was conducted in November 2014 to identify prospective human studies of body weight change and all-cause mortality in noninstitutionalized older adults, defined as individuals 60 years and older (Figure 1). Search term combinations included: (anthropometr* or body weight* or body mass index or body weight change* or weight loss* or weight gain*) AND (mortalit* or death* or survival rate*) AND (aging* or elder* or geriatric* or older adult*). For Pub Med (MEDLINE), the following mesh terms were used and appropriately combined: anthropometry, body weight, body mass index, body weight changes, body weight changes, weight loss, weight gain, mortality, death, survival rate, humans, middle aged, aged, and aged, 80 and over. Reference lists of all selected studies were examined to identify other relevant articles.
Selection Criteria

The search included only English language studies published through November 2014. The inclusion criteria covered all prospective studies with (1) body weight change (also in terms of changes in body mass index) as one of the main predictors, (2) all-cause mortality as one of the main outcomes, (3) noninstitutionalized adults 60 years and older at baseline, and (4) relative risk (risk ratio, hazard ratio, or odds ratio) of all-cause mortality and associated 95% confidence interval for weight changes relative to a reference group. We did not include editorial letters, commentaries, systematic reviews, meta-analyses, and conference abstracts.
Data Extraction

Data from all included studies were extracted independently by one reviewer (F.W.C.) and verified by a second reviewer (X.G.) with consensus secured by discussion. Extracted data included first author, year (reference), country, cohort (if applicable), sample size (number of deaths), sex, baseline age in years (range/mean/median), years of follow-up (max/mean/median), weight change group (measured/self-reported; time period of the weight change), relative risk: risk ratio, hazard ratio, or odds ratio (95% confidence interval), and data adjustment.

Quality Assessment

One reviewer (F.W.C.) independently examined the methodological quality of all included studies using the Newcastle-Ottawa scale (NOS) (19) and a second reviewer (X.G.) reviewed the NOS points given (Table 1). Any discrepancies were resolved by discussion before scores were finalized. We distinguished quality assessment (19) by study design: cohort study and case-control study. Cohort studies were evaluated by three main categories: cohort selection (0–4 points), cohort comparability (0–2 points), and outcome assessment (0–3 points). The single case-control study was assessed by three main categories: selection of cases and controls (0–4 points), comparability of cases and controls (0–2 points), and exposure ascertainment (0–3 points). A maximum of 9 points were allotted for each study; receiving 7 or more points represented high methodological quality (19–22).

Statistical Analysis

Weight change was categorized into three main groups: weight loss (9, 10, 23–37), weight gain (9, 10, 24, 25, 27, 28, 30–37), and weight fluctuation (9, 10, 29) (Table 1). Thus, there were a total of three full-group meta-analyses performed. Four publications (10, 29, 36, 37) reported sex-specific relative risk (RR). In this situation, we combined sex-specific estimates by using a within-study fixed-effects meta-analysis to derive pooled estimates for the full analysis. Similarly, for publications (25, 28, 29, 33, 36, 37) that had two weight loss subgroups or two weight gain subgroups, both estimates were pooled together using a within-study fixed-effects meta-analysis and included in the appropriate full group analysis. A previous meta-analysis has also utilized this approach (12). The most fully adjusted estimate was selected when both crude and adjusted RRs were reported.

To normalize the distributions, reported RRs were converted to their natural logarithms. Standard errors (SEs) were calculated with the following equation (38): $SE = \ln(\frac{\text{upper 95\% CI}}{\text{lower 95\% CI}})/(2 \times \text{1.96})$. For each of the three full analyses, we used (1) random-effects model to account for both
<table>
<thead>
<tr>
<th>First author, year (Ref)</th>
<th>Country, Cohort (If applicable)</th>
<th>Sample size (No. of deaths)</th>
<th>Sex</th>
<th>Baseline age (Years) (Range/ mean/ median)</th>
<th>Years of follow-up (Max or range)/ mean/ median</th>
<th>Weight change group (Measured/ self-reported; time period of the weight change)</th>
<th>Relative risk: risk ratio, hazard ratio, or odds ratio (95% confidence interval)</th>
<th>Data adjustment</th>
<th>Study quality*</th>
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<tbody>
<tr>
<td>Ho, 1994 (35)</td>
<td>Hong Kong</td>
<td>374 (35) F</td>
<td>≥70/ 79.7/</td>
<td>1.3/1.3/</td>
<td>Weight loss group: lost &gt;2kg</td>
<td>Reference group: no change</td>
<td>4.8 (1.3–18.4)</td>
<td>Age, reported health status, number of health conditions (cancer except skin, arthritis, diabetes, bronchitis, asthma, ulcer, cirrhosis, gallbladder, hypertension, and cardiovascular—including heart attack, heart condition, angina, transient ischemic attack, or stroke), place of residence, income, BMI</td>
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<td>Wallace, 1995 (23)</td>
<td>US</td>
<td>229 (35) M</td>
<td>≥65/ 72.9/</td>
<td>25/</td>
<td>Weight loss group: lost ≥4% (between 0 and 1st yr OR between 1st and 2nd yr)</td>
<td>Reference group: within ±4% (between 0 and 1st yr and between 1st and 2nd yr)</td>
<td>2.83 (1.38–5.81)</td>
<td>Age, BMI, tobacco use, hypertension, Sickness Impact Profile scores, self-rated health, cholesterol and albumin levels</td>
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<th>Data adjustment</th>
<th>Study quality&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>Dey, 2001 (37)</td>
<td>Sweden</td>
<td>2,405 (1,333) M,F</td>
<td>70/70/70</td>
<td>10/1/1</td>
<td>1.62 (1.21–2.16) Weight loss group 1: lost ≥10% 1.11 (0.77–1.59) Weight loss group 2: lost 5%–9.9% Reference group: lost 0%–4.9% 1.03 (0.69–1.54) Weight gain group 1: gained 0%–4.9% 1.01 (0.72–1.42) Weight gain group 2: gained ≥5%</td>
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<td>Birth cohorts, smoking habits at or before age 70 *Excluded subjects who had cancer at or before age 70</td>
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<td>Newman, 2001 (24)</td>
<td>US</td>
<td>4,714 (388) M,F ≥65/74.2/</td>
<td>1–3/1/</td>
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<td>1.67 (1.29–2.15) Weight loss group: lost ≥5% 1.0 (reference) Weight gain group: gained ≥5% (Measured; 5yr) 0.94 (0.65–1.46)</td>
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<sup>a</sup>Age, sex, race, digit symbol score, number of medications, gastrointestinal disease, log of pack years of smoking, waist circumference, mobility-impairment.
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<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Population Details</th>
<th>Sample Size</th>
<th>Gender Distribution</th>
<th>Age</th>
<th>Sex, Current Smoking Status, Presence of Myocardial Infarction, Diabetes, or Strokes at Baseline</th>
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<td>Somes, 2002 (25)</td>
<td>US, Systolic Hypertension in the Elderly Program</td>
<td>4,485 (351) M,F ≥60/ 4.5/</td>
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<td>4.92 (3.55–6.83) Age, sex, current smoking status, presence of myocardial infarction, diabetes, or strokes at baseline</td>
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<td>Crotty, 2002 (26)</td>
<td>Australia, Australian Longitudinal Study of Ageing</td>
<td>1,396 (265) M,F ≥70/ 77.9/</td>
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<td>2.53 (1.37–4.67) Age, sex, marital status, smoking status, alcohol status, self-rated health, number of comorbid conditions, independence in basic activities of daily living, baseline BMI</td>
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<td>Amador, 2005 (27)</td>
<td>US, Hispanic Established Population for the Epidemiological Study of the Elderly</td>
<td>1749 (361) M,F ≥65/ 74.4/</td>
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<td>1.41 (1.03–1.95) Age, sex, BMI, waist circumference, medical conditions, high depressive symptoms (Center for Epidemiologic Studies Depression Scale ≥16), 2-year change in handgrip strength change, 2-year change in summary performance score of lower body function, smoking status, ADL disability and IADL disability</td>
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<th>First author, year (Ref)</th>
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<th>Weight change group (Measured/self-reported; time period of the weight change)</th>
<th>Relative risk: risk ratio, hazard ratio, or odds ratio (95% confidence interval)</th>
<th>Data adjustment</th>
<th>Study quality*</th>
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<td>Keller, 2005 (28)</td>
<td>Canada: Canadian Study of Health and Aging</td>
<td>539 (207)</td>
<td>M,F</td>
<td>≥65//</td>
<td>5//</td>
<td>Weight loss group 1: lost ≥2 BMI units</td>
<td>2.10 (1.17–3.81) Age, BMI, education, marital status, smoking, cognitive impairment</td>
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<td>Weight loss group 2: lost 0 to &lt;2 BMI units</td>
<td>1.01 (0.55–1.87)</td>
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<td>Reference group: gained 0 to &lt; 2 BMI units</td>
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<td>Weight gain group: gained ≥2 BMI units (Measured; 5 yr) Men - Weight Loss</td>
<td>1.35 (0.71–2.58) Age, smoking status, concomitant diseases</td>
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<td>Weight loss group 1: lost ≥1% / yr</td>
<td>2.6 (19–3.7)</td>
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<td>Weight loss group 2: lost 0.5 to 0.9% /yr</td>
<td>1.3 (0.9–2.0)</td>
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<td>Reference group: lost &lt;0.5% / yr Women - Weight Loss</td>
<td>1 (reference)</td>
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<td>Weight loss group 1: lost ≥1% / yr</td>
<td>2.2 (1.7–2.9) Age, smoking status, concomitant diseases</td>
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<td>Weight loss group 2: lost 0.5 to 0.9% /yr</td>
<td>1.2 (0.8–1.7)</td>
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<td>Reference group: lost &lt;0.5% /yr Men - Weight fluctuation</td>
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<td>Reference group: &lt;3% (coefficient variation)</td>
<td>1 (reference)</td>
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<td>Nguyen, 2007 (29)</td>
<td>Australia: Dubbo Osteoporosis Epidemiology Study</td>
<td>1,703 (547)</td>
<td>M,F</td>
<td>≥60/70/</td>
<td>9-14//13</td>
<td>Weight loss group 1: lost ≥1% / yr</td>
<td>2.6 (19–3.7) Age, BMI, education, marital status, smoking, cognitive impairment</td>
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<td>Weight loss group 2: lost 0.5 to 0.9% /yr</td>
<td>1.3 (0.9–2.0) Age, smoking status, concomitant diseases</td>
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<td>Reference group: lost &lt;0.5% / yr Women - Weight Loss</td>
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<td>Weight loss group 1: lost ≥1% / yr</td>
<td>2.2 (1.7–2.9) Age, smoking status, concomitant diseases</td>
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<td>Reference group: lost &lt;0.5% /yr Men - Weight fluctuation</td>
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<td>Reference group: &lt;3% (coefficient variation)</td>
<td>1 (reference)</td>
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<td>Study</td>
<td>Country</td>
<td>Population</td>
<td>Age</td>
<td>Sex</td>
<td>BMI</td>
<td>Reference</td>
<td>Weight fluctuation group:</td>
<td>Weight loss group:</td>
<td>Weight gain group:</td>
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<tr>
<td>Luchsinger, 2008 (30)</td>
<td>US</td>
<td>1,113 (357)</td>
<td>M,F</td>
<td>≥65/78.3</td>
<td>/7/</td>
<td>1.5 (1.1–2.0)</td>
<td>≥5% (coefficient variation)</td>
<td>1.5 (1.2–1.9)</td>
<td>1.10 (0.89–1.36)</td>
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<tr>
<td>Arnold, 2010 (9)</td>
<td>US: Cardiovascular Health Study</td>
<td>3,278 (1,072)</td>
<td>M,F</td>
<td>≥65/80</td>
<td>/7/</td>
<td>1.58 (1.33–1.88)</td>
<td>≥5% from prior or from baseline</td>
<td>1.58 (1.33–1.88)</td>
<td>1.10 (0.89–1.36)</td>
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| First author, year (Ref) | Country, Cohort (If applicable) | Sample size (No. of deaths) | Sex | Baseline age (Years) (Range/mean/median) If available | Years of follow-up (Max or range)/mean/median) If available | Weight change group (Measured/self-reported; time period of the weight change) | Relative risk: risk ratio, hazard ratio, or odds ratio (95% confidence interval) | Data adjustment | Study quality
|-------------------------|---------------------------------|-----------------------------|-----|------------------------------------------------------|-------------------------------------------------------------|---------------------------------------------------------------------------------|------------------------------------------------------------------|-----------------|----------------|
| Nanri, 2010 (36)        | Japan: Japan Public Health Centered-Based Prospective Study | 80,311 (4,232) This is the total of 45–75 combined. | M,F 45–75//8.7/ Subgroup analysis for ≥60 | N        | Weight fluctuation group: lost and gained ≥5% — assessed annually by comparing current weight with weight in the prior yr and initial yr (Measured; weight change category already calculated per year) | 1.66 (1.38–2.00) | Age, study area, body mass index, alcohol consumption, leisure-time physical activity, history of hypertension and diabetes mellitus, smoking | 7
|                         |                                 |                             |     | Weight loss group 1: lost ≥5 kg                       | 1.58 (1.37–1.82) | 1 (reference) | 4
|                         |                                 |                             |     | Weight loss group 2: lost 2.5 to 4.9 kg               | 1.34 (1.15–1.55) | 1 (reference) | 4
|                         |                                 |                             |     | Reference group: within ±2.4 kg                       | 1 (reference) | 1 (reference) | 4
|                         |                                 |                             |     | Weight gain group 1: gained 2.5 to 4.9 kg            | 1.02 (0.84–1.23) | 1 (reference) | 4
|                         |                                 |                             |     | Weight gain group 2: gained ≥5 kg                    | 1.49 (1.26–1.76) | 1 (reference) | 4
|                         |                                 |                             |     | Women Weight loss group 1: lost ≥5 kg                 | 1.68 (1.39–2.03) | 1 (reference) | 4
|                         |                                 |                             |     | Weight loss group 2: lost 2.5 to 4.9 kg               | 1.23 (1.00–1.51) | 1 (reference) | 4
|                         |                                 |                             |     | Reference group: within ±2.4 kg                       | 1 (reference) | 1 (reference) | 4
|                         |                                 |                             |     |                                                        |                 | 1 (reference) | 4

This is the total of 45–75 combined.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country/Cohort Description</th>
<th>Control:</th>
<th>Case:</th>
<th>Weight Gain Group 1:</th>
<th>Weight Gain Group 2:</th>
<th>Weight Loss Group:</th>
<th>Reference Group:</th>
<th>Weight Gain Group 1:</th>
<th>Weight Gain Group 2:</th>
</tr>
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<tbody>
<tr>
<td>Bamia, 2010</td>
<td>Europe—European Prospective Investigation into Cancer and Nutrition</td>
<td>M,F ≥60/65</td>
<td>4,942</td>
<td>≤6/65.4/</td>
<td>≥13.6/9.8/</td>
<td>1.2</td>
<td>1.14 (0.85–1.53)</td>
<td>1.26 (0.99–1.61)</td>
<td>1.14 (0.85–1.53)</td>
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<tr>
<td>Lee, 2011</td>
<td>US: Osteoporotic Fractures in Men</td>
<td>M 65–93</td>
<td>4,331</td>
<td>72.8</td>
<td>0.03–4.2/3.2/</td>
<td>1.84 (1.50–2.26)</td>
<td>1.84 (1.50–2.26)</td>
<td>1.04 (0.71–1.51)</td>
<td>1.15 (0.98–1.37)</td>
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<tr>
<td>de Hollander et al., 2013</td>
<td>Europe: Survey in Europe on Nutrition and the Elderly, a Concerted Action</td>
<td>M,F 70–77</td>
<td>1,053</td>
<td>72.9</td>
<td>6/6/</td>
<td>1.48 (0.99–2.20)</td>
<td>1.48 (0.99–2.20)</td>
<td>1.25 (0.84–1.88)</td>
<td>1.14 (0.76–1.72)</td>
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<th>Baseline age (Years) (Range/mean/median) If available</th>
<th>Years of follow-up (Max or range)/ mean/median) If available</th>
<th>Weight change group (Measured/ self-reported; time period of the weight change)</th>
<th>Relative risk: risk ratio, hazard ratio, or odds ratio (95% confidence interval)</th>
<th>Data adjustment</th>
<th>Study quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dahl et al., 2013 (34)</td>
<td>Sweden; OCTO-twin, GENDER, NONA</td>
<td>882 (667)</td>
<td>M,F</td>
<td>70–95/80.1/ 18/ //</td>
<td></td>
<td>Weight gain group 2: gained ≥2.8 kg/yr (Measured; weight change category already calculated per year)</td>
<td>0.94 (0.62–1.41)</td>
<td>Age, sex, education, multimorbidity, BMI</td>
<td>6</td>
</tr>
<tr>
<td>Murphy et al., 2014 (10)</td>
<td>US: Health, Aging, and Body Composition</td>
<td>1975 (698)</td>
<td>M,F</td>
<td>70–79/78.1/ 8/ //</td>
<td></td>
<td>Weight loss group: loss ≥5% Reference group: within ±5%</td>
<td>1.65 (1.34–2.04) Age, race, education, study site, BMI, smoking status, physical activity, depressive symptoms, cancer, diabetes, mellitus, hip fracture, hypertension, myocardial infarction, stroke, incidence of hospitalization, days of hospitalization, year 6 lean mass, year 6 fat mass, percentage of change in lean mass, percentage change in fat mass</td>
<td>1 (reference)</td>
<td>8</td>
</tr>
</tbody>
</table>
Weight fluctuation group: lost or gained ≥5% assessed annually by comparing current weight with weight in the prior yr

| Women | Weight loss group: lost ≥5% from prior year or from baseline to year 6 (last weight measurement) | 1.30 (0.92–1.83) |
| Reference group: within ±5% from prior year or from baseline to year 6 (last weight measurement) | 1 (reference) |
| Weight gain group: gained ≥5% from prior year or from baseline to year 6 (last weight measurement) | 1.37 (0.90–2.08) |

Study quality was assessed by the Newcastle-Ottawa scale (NOS) (19).
within- and between-study variation and (2) metainf command (meta influence analysis) to investigate the influence of each individual estimate (39).

To examine the robustness of our observations, we conducted sensitivity analyses for each full meta-analysis that imposed stricter inclusion criteria. The Institute of Medicine characterized “weight loss maintenance as losing at least 5% of body weight, or reducing body mass index (BMI) by at least 1 unit, and keeping weight below this minimum amount for at least 1 year” (40, 41). Thus, we selected this value for use in our meta-analyses. We therefore included only RR estimates from weight change groups of at least 5% weight loss or -1 BMI unit per year (9, 10, 26, 27). For studies (23, 24, 26–28, 32, 34–37) that did not provide weight change per year, weight change was divided by weight change period, which was then used to determine whether it met the criteria for the sensitivity analysis. Weight gain (9, 10, 27) (weight gain of at least 5% or +1 BMI unit per year) and weight fluctuation (9, 10) (weight loss or gain of at least 5% or -1 BMI unit per year by comparing current weight with weight in the prior year) sensitivity analyses utilized the same approach.

Furthermore, we conducted five subgroup analyses for each of the full analyses: average baseline age, length of follow-up, location, methodological quality, and sex-specific; the differences between subgroups were also examined by the meta-regression method. First, to investigate the impact of average baseline age on the results, we separated the studies into two groups using median average baseline age of 74.3 years as a cutoff point (average baseline age between 60.0 and 74.3 years (23, 24, 29, 31–33, 37) and average baseline age greater than 74.3 years (9, 10, 26, 27, 30, 34, 35)). Second, since the length of follow up may have an influence on the outcomes, we categorized the studies into two groups using the median follow-up period of 6 years as a cutoff point (follow-up 6 years or less (23–28, 32, 33, 35) and follow-up longer than 6 years (9, 10, 29–31, 34, 36, 37)). Third, to examine whether geographic region influenced the results, we divided the studies into Western countries (9, 10, 23–34, 37) and Asian countries (35, 36). Fourth, we ran separate analyses for studies with low (<7 points on the NOS) (23–26, 29, 31, 34) and high (≥7 points on the NOS) (9, 10, 27, 28, 30, 32, 33, 35–37) study quality to examine whether methodological quality impacted our results. Lastly, to investigate whether there was a sex difference in the relationship between weight change and all-cause mortality, we performed subgroup analyses with available sex-specific estimates (10, 23, 29, 32, 35–37).

Heterogeneity among studies was quantified with Cochran’s Q and $I^2$ statistics (42). $P$ value of less than 0.10 in Cochran’s Q statistic reflects statistically significant heterogeneity (42). $I^2$ illustrates the proportion of total variability attributed by between-study variation; $I^2$ values of 25%, 50%, and 75% represent low, moderate, and high heterogeneity, respectively (42). Publication bias was evaluated with funnel plots and with the Begg and Egger
tests; statistical significance was considered at $p < 0.1$ (43,44). All meta-analyses were performed on the natural log scale and graphs were created in Stata version 13.0 (Stata-Corp, College Station, TX).

RESULTS

Study Selection

We identified 10,201 potential study publications with 298 duplicates via an electronic literature search (Figure 1). We excluded 9522 records based on review of the title and/or abstract, leaving 381 for full text review. We further excluded 365 articles after full text review because they failed to meet our inclusion criteria. This resulted in 16 articles with one additional eligible article identified from the reference lists. A total of 17 publications were therefore included in the final analysis.

Study Characteristics

Table 1 summarizes the characteristics of the 17 included studies from both Western (9, 10, 23–34, 37) and Asian (35, 36) countries. Follow-up periods ranged from 1.3 (35) to 18 (34) years. Samples sizes and the number of all-cause mortality cases ranged from 229 (23) to 6654 (31) and from 35 (23, 35) to 1712 (31), respectively, except for one study (36) that did not provide sample size and mortality information for participants ≥60 years. One study (31) used a case-control design and the others (9, 10, 23–30, 32–37) were cohort studies.

Ten (9, 10, 27, 28, 30, 32, 33, 35–37) of 17 studies were of high methodological quality, as defined by receiving 7 or more points on the Newcastle-Ottawa Scale (NOS) (Table 1). Some of the common reasons for poor scores were: utilized self-reported weight and height measurements, did not control for some important factors (e.g., age, sex, baseline body mass index or weight, smoking status, and comorbidity), and did not specify assessment of outcome or loss to follow-up.

Weight Loss and All-Cause Mortality

All 17 studies examined the relationship between weight loss and all-cause mortality. The overall pooled relative risk of all-cause mortality for the weight loss group was 1.67 (95% CI, 1.51–1.85) (Figure 2a). There was statistically significant heterogeneity among the estimates reported by the included studies (Q test, $p < 0.001$; $I^2 = 69\%$). We performed subgroup analyses to examine the potential impacts of study characteristics and tested the differences between subgroups by the meta-regression method. Only study quality showed a statistically significant effect on the pooled RR of all-cause mortality associated with weight loss ($p = 0.005$); other study characteristics, including average baseline age, duration of follow up, geographical region, and sex,
were not significant ($p > 0.05$ for all) (Table 2). Omitting one study at a time did not substantially change the overall result (data not shown). No evidence of publication bias was observed (Egger’s test, $p = 0.09$; Begg’s test, $p = 0.34$) (Figure 3a).

**FIGURE 2** Association between weight loss (Figure 2a), weight gain (Figure 2b), and weight fluctuation (Figure 2c) and all-cause mortality among individuals $\geq 60$ years.

were not significant ($p > 0.05$ for all) (Table 2). Omitting one study at a time did not substantially change the overall result (data not shown). No evidence of publication bias was observed (Egger’s test, $p = 0.09$; Begg’s test, $p = 0.34$) (Figure 3a).
| Study characteristics | Weight loss | | | Weight gain | | |
|-----------------------|-------------|---|---|-------------|---|
|                       | # of studies | Reference | RR (95% CI) | Pdiff | # of studies | Reference | RR (95% CI) | Pdiff |
| Average Baseline Age  |             |             |             |       |             |             |             |       |
| ≤74.3 years           | 7           | 23,24,29,31–33,37 | 1.68 (1.54–1.84) | 0.12  | 5           | 24,31–33,37 | 1.10 (0.99–1.23) | 0.25  |
| >74.3 years           | 7           | 9,10,26,27,30,34,35 | 1.54 (1.35–1.75) |       | 6           | 9,10,27,30,34,35 | 1.21 (1.05–1.40) |       |
| Follow Up Length      |             |             |             |       |             |             |             |       |
| ≤6 years              | 9           | 23–28,32,33,35 | 1.91 (1.52–2.40) | 0.07  | 7           | 24,25,27,28,32,33,35 | 1.20 (0.90–1.61) | 0.89  |
| >6 years              | 8           | 9,10,29–31,34,36,37 | 1.56 (1.45–1.67) |       | 7           | 9,10,30,31,34,36,37 | 1.21 (1.13–1.30) |       |
| Geographical Region   |             |             |             |       |             |             |             |       |
| Western countries     | 15          | 9,10,23–34,37 | 1.69 (1.51–1.88) | 0.70  | 12          | 9,10,24,25,27,28,30–34,37 | 1.21 (1.08–1.36) | 0.47  |
| Asian countries       | 2           | 35,36       | 2.19 (0.72–6.60) |       | 2           | 35,36       | 1.25 (1.12–1.38) |       |
| Study Quality         |             |             |             |       |             |             |             |       |
| <7 NOS points         | 7           | 23–26,29,31,34 | 1.98 (1.64–2.38) | 0.005 | 4           | 24,25,31,34 | 1.40 (1.01–1.96) | 0.10  |
| ≥7 NOS points         | 10          | 9,10,27,28,30,32,33,35–37 | 1.50 (1.40–1.61) |       | 10          | 9,10,27,28,30,32,33,35–37 | 1.18 (1.10–1.27) |       |
| Sex                   |             |             |             |       |             |             |             |       |
| Men                   | 6           | 10,23,29,32,36,37 | 1.60 (1.37–1.86) | 0.94  | 4           | 10,32,36,37 | 1.21 (1.09–1.34) | 0.71  |
| Women                 | 5           | 10,29,35–37  | 1.60 (1.36–1.89) |       | 4           | 10,35–37   | 1.25 (1.08–1.45) |       |

RR, relative risk; 95% CI = 95% confidence interval; $P_{diff} = P_{difference}$.

3 studies (25, 28, 36) were excluded because of inadequate information on average baseline age.

1 = Western countries: United States, Canada, Europe, and Australia; 0 = Asian countries: Hong Kong and Japan.
FIGURE 3 Funnel plot of study weights against log ratio of all-cause mortality for weight loss (Figure 3a), weight gain (Figure 3b), and weight fluctuation (Figure 3c) groups among individuals ≥60 year.
Four studies (9, 10, 26, 27) met the criteria for the sensitivity analysis (RR estimates from weight change group of at least 5% weight loss or −1 BMI unit per year) and they resulted in a pooled estimate of RR = 1.49 (95% CI, 1.24–1.80).

Weight Gain and All-Cause Mortality

A total of 14 studies (9, 10, 24, 25, 27, 28, 30–37) investigated the association between weight gain and all-cause mortality. The overall pooled RR of all-cause mortality for the weight gain group was 1.21 (95% CI, 1.09–1.33) (Figure 2b). There was moderate heterogeneity among the estimates reported by the included studies (Q test, \( p = 0.03; \ I^2 = 46\% \)). None of the study characteristics, including average baseline age, duration of follow up, geographical region, study quality, and sex, had statistically significant effects on the pooled RR for all-cause mortality associated with weight gain (\( p > 0.05 \) for all) (Table 2). Omitting one study at a time did not alter the overall pooled estimate (data not shown). No evidence of publication bias was observed (Egger’s test, \( p = 0.996; \ Begg’s \text{ test, } p = 0.51 \) (Figure 3b).

Three studies (9, 10, 27) met the criteria for the sensitivity analysis (RR estimates from weight change group of at least 5% weight gain or +1 BMI unit per year) and they resulted in a pooled estimate of RR = 1.14 (95% CI, 0.96–1.35).

Weight Fluctuation and All-Cause Mortality

Three studies (9, 10, 29) reported the association between weight fluctuation and all-cause mortality. The overall pooled relative risk of all-cause mortality for the weight fluctuation group was 1.53 (95% CI, 1.36–1.72) (Figure 2c). There was no significant heterogeneity among the estimates reported by the included studies (Q test, \( p = 0.43; \ I^2 = 0\% \)). The small number of studies in this group precluded any meaningful use of subgroup analyses and meta-regression to examine the effects of study characteristics. Omitting one study at the time did not substantially change the overall pooled estimate (data not shown). No evidence of publication bias was noted (Egger’s test, \( p = 0.828; \ Begg’s \text{ test, } p = 1.00 \) (Figure 3c).

Two studies (9, 10) met the criteria for the sensitivity analysis (RR estimates from weight change group of at least 5% weight loss/gain or −/ +1 BMI unit per year by comparing current weight with weight in the prior year) and they resulted in a pooled estimate of RR = 1.61 (95% CI, 1.39–1.86).

DISCUSSION

This study combined all-cause mortality estimates in older adults with weight change from observational cohort studies in both Western and Asian
countries. Compared to individuals with weight change (e.g., weight loss, gain, and fluctuation), weight stable older adults had lower all-cause mortality risk. Similar results were observed when we imposed stricter criteria for sensitivity analyses.

Weight loss was associated with higher all-cause mortality risk in our meta-analyses. Although prior studies were not focused exclusively on persons aged 60 years and older, previous systematic reviews and meta-analyses also found higher all-cause mortality risk associated with weight loss for mixed populations of middle-aged and older adults (12–14). Subgroup analysis on the duration of follow-up revealed a more detrimental effect on shorter-term mortality, possibly reflecting terminal decline or underlying disease (45). Alley and colleagues observed accelerated weight loss between three to nine years before death depending on the cause of mortality (45). In our meta-analysis, the log RR for all-cause mortality was significantly lower in publications with higher study quality (≥7 NOS points). Since most high quality studies have longer follow-up period, this inverse relationship is consistent with that of duration of follow-up.

We found that weight gain was also associated with increased risk of all-cause mortality but the effect appeared to be milder than that of weight loss. Andres and colleagues reported highest mortality rates in adults (aged 20 to 99 at baseline) with severe weight gain and lowest mortality rates in those with moderate weight gain (14). Current literature does not seem to suggest a major impact of mild weight gain on all-cause mortality among older adults but implications should be interpreted with caution. The mortality risk associated with weight gain seemed to subside as the length of follow-up decreased.

We also observed that weight fluctuation was associated with higher risk of mortality. However, the small number of studies did not allow for further investigation on the impact of study characteristics. Lee and associates observed that older individuals with weight fluctuation did not regain the lean mass that was lost during the weight loss period in the weight regain period, which may contribute to the observed higher mortality risk (46).

There are several strengths to the meta-analyses that we have conducted. First, we utilized a comprehensive search strategy protocol and followed the MOOSE guidelines (18, 47). Second, the use of weight change, rather than a one-time anthropometric measurement (e.g., initial BMI), may serve as a more descriptive and better predictor for older individuals in term of health outcomes and longevity (7, 25, 35). Third, we used the Newcastle-Ottawa scale as a standardized approach to assess the quality of all included studies with different cofounders or covariates in the adjusted models. For instance, baseline BMI is associated with both weight change and mortality and could confound the observed association. Thus, we included baseline BMI as one of the items in the Newcastle-Ottawa scale for study quality. Fourth, since the definition of weight change differed
among studies, we used a predefined weight change threshold from the Institute of Medicine in our sensitivity analysis (40, 41). Fifth, the majority of the included studies had a mean BMI in the overweight range (25.0 kg/m² to < 30.0 kg/m²), which is representative of the typical BMI among US older adults (4–6). Thus we were reassured in our desire to represent the general population of older adults living in the community rather than just the underweight and frail older adults, who are known to be quite adversely affected by weight change (48).

Several limitations should be considered when interpreting our outcomes. First, we did not account for weight change intentionality as most included studies either did not collect or include this information in their analyses. Intentionality likely has a role in the relationship between weight change, especially weight loss, and all-cause mortality. Nonvolitional weight loss often represents underlying illness(es) or inflammatory conditions, which may increase mortality risk (49). To address this issue, some studies excluded persons with early deaths as part of their sensitivity analyses and reported a slight attenuation in association but results remained significant (25, 31, 33) except for two studies (30, 36). While it is logical to associate desirable outcomes with volitional weight loss, results have been equivocal with observational studies (23, 32). Moreover, distinguishing volitional from nonvolitional weight loss is difficult (10). However, a recent meta-analysis (50) of weight loss intervention trials (mean age of 52 years) showed a potential benefit of volitional weight loss. Of the 15 included studies, only three focused on older adults (mean baseline age >65 years); the first study (51) reported a significant benefit for weight loss, the second study (52) showed a nonsignificant benefit for weight loss, and the third study (53) did not observe a difference. Second, our results addressed only findings related to change in weight and no other anthropometric measurements (e.g., waist circumference and waist-to-hip ratio). Loss of lean body mass may be a powerful predictor of increased mortality risk in older persons (32) but such measures are well beyond the scope of our present analyses. Although other measurements may better characterize obesity or changes in body composition, many are not practical or feasible in population studies or routine clinical settings. Hence, investigating the relationship between weight change and all-cause mortality becomes a priority for public health policy change. Third, we focused our outcome on all-cause mortality instead of cause-specific mortality or morbidity, which may have different relationships with weight change. Further studies are needed to explore these relationships. Fourth, the small number of studies from Asian countries prohibited any meaningful conclusion on the potential differences between Western and Asian countries. It is also important to note that there is considerable ethnic and racial diversity within these Western studies (e.g., Hispanic and African American) (10, 27). In addition, we applied a Western weight change threshold to Asian studies, which may not be appropriate. Fifth, only three
included studies examined the relationship between weight fluctuation and all-cause mortality. Although the pooled RR detected a significant result, more studies with longer follow-up period are needed because there is less chance for weight fluctuation with short follow-up duration. Furthermore, there was wide variation in how weight fluctuation was defined. For instance, two studies (9, 10) defined weight fluctuation as “lost or gained ≥5% assessed annually by comparing current weight with weight in the prior year,” while one study (29) defined it as “≥3% (coefficient variation).” Sixth, although we used the Institute of Medicine threshold for weight change, which defines “weight loss maintenance as losing at least 5% of body weight, or reducing BMI by at least 1 unit, and keeping weight below this minimum amount for at least 1 year” (40, 41), it is important to note that 5% weight change and 1 BMI unit change are not equivalent. Moreover, the included studies reported weight loss over the study period or per year. Thus, more studies are warranted to further clarify the best approach to studying the association between weight change and all-cause mortality.

CONCLUSIONS

Overall, we observed a higher mortality risk with weight change among non-institutionalized adults 60 years and older. Although current results suggest a potential adverse effect of weight change on all-cause mortality among the aging population, more research is warranted to provide the specificity needed to develop meaningful public health and clinical guidelines. Future studies should consider using a more standardized weight change definition and comprehensive subgroup analysis (e.g., by baseline BMI category) to enhance comparability and specificity. Moreover, recognizing the characteristics that discern survivors from non-survivors should be helpful to guide clinicians and public health practitioners in detecting at-risk individuals for early prevention.

TAKE AWAY POINTS

• Based on this meta-analysis, weight loss, weight gain, and weight fluctuation were all found to be associated with higher mortality risk among community-dwelling adults 60 years and older.
• Increased mortality with weight loss has been previously recognized. Increased mortality with weight gain is less well recognized and, while the effect was milder than for weight loss, deserves further exploration. This is also true for weight fluctuation, which has previously been suspected of being detrimental but has not been well studied.
• Future studies should consider using a more standardized weight change definition and comprehensive subgroup analysis (e.g., by baseline BMI
category) to enhance comparability and specificity needed to develop meaningful public health and clinical guidelines.

FUNDING

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REFERENCES

Chapter 7

CONCLUSIONS
SUMMARY OF RESEARCH FINDINGS AND IMPLICATIONS

The studies in this dissertation research project were designed to further understand the obesity paradox, which describes the inverse association between body mass index (BMI) and all-cause mortality among older persons. These studies 1) examined the association between baseline BMI and all-cause mortality; 2) investigated the joint effects of BMI class and metabolic health in relation to all-cause mortality; and 3) used conditional inference tree analysis to construct a risk stratification algorithm for risk of developing functional decline, based on BMI and other potential risk factors. In addition, we performed a meta-analysis of observational cohort studies to examine current literature on the association between weight change (weight loss, weight gain, and weight fluctuation) and all-cause mortality among community-dwelling adults aged 60 years or older.

Chapter 3 addressed objective 1, examining the association between baseline BMI and all-cause mortality. When modeling BMI as a continuous variable using a restricted cubic spline approach, we observed a U-shaped association between BMI and all-cause mortality \((P\text{-non-linearity}<0.001)\). This analysis was adjusted for age, sex, smoking status, alcohol drinker, clinical laboratory values, disease burden, and other related health factors. Relative to a BMI of 23.0 kg/m\(^2\), the nadir of the curve (i.e., BMI range associated with significantly lower mortality risk) was between 23.3 and 36.0 kg/m\(^2\) and lowest risk was between 28.0 and 30.0 kg/m\(^2\). Results were similar when we treated BMI as a categorical variable according to the National Institutes of Health (NIH) BMI guidelines. Compared to those with a BMI between 18.5 and 24.9 kg/m\(^2\), individuals with a BMI less than 18.5 kg/m\(^2\) had an adjusted hazard ratio (HR) of 3.35 (95% CI: 1.88,
5.96) for all-cause mortality risk. However, this mortality risk was reduced among those with overweight (adjusted HR: 0.80; 95% CI: 0.71, 0.90) or class I obesity (adjusted HR: 0.78; 95% CI: 0.69, 0.89) and participants with class II or III obesity did not have a significantly higher all-cause mortality risk (class II obesity – adjusted HR: 0.96; 95% CI: 0.81, 1.12; class III obesity – adjusted HR: 1.17; 95% CI: 0.93, 1.47).

An important goal of objective 1 was to address some of the methodological issues that contribute to the controversy that surrounds the obesity paradox. Residual confounding by smoking and reverse causation due to disease burden, smoking, and early deaths must be considered. Therefore, we addressed these crucial issues by conducting multiple sensitivity analyses that: 1) excluded those who smoked and had any identified chronic disease burden, 2) used propensity score weights that were generated by generalized boosted models as an alternative method to minimize the impact of potential confounders, 3) excluded those who smoked and had died within the first two years of follow-up, and 4) excluded those who smoked and had died within the first five years of follow-up. However, findings from these sensitivity analyses remained consistent, supporting the obesity paradox among older persons and suggesting that methodological issues could not fully explain this phenomenon.

There are several potential mechanisms to explain the obesity paradox. First, excess fat could serve as a metabolic reserve during injury or illness (1). Second, those who survived to old age may be less susceptible to the harmful effects of overweight or obesity (2). This “selective survival” bias could have attenuated the association between higher BMI and all-cause mortality risk (1). Third, excess adiposity may be protective against osteoporotic fracture. Individuals with higher BMI tend to have greater bone
mineral density (3). Excess body fat, especially around the hip area, could also serve as a protective padding during falls (4). Fourth, older persons may be less affected by excess body fat because the lipolytic activity in visceral fat appears to be less activated by noradrenaline as age increases (5). Fifth, although this may not directly contribute to the obesity paradox, physicians tend to be more diligent during surgery or prescribe more aggressive treatments for patients with overweight or obesity (6). Lastly, BMI is not a perfect measurement for adiposity among older adults. However, Al Snih et al. noted that “the same methods that found little association between elevated BMI and subsequent mortality found a strong association between elevated BMI and disability” (7).

Chapter 4 addressed objective 2, investigating the joint effects of BMI class and metabolic health in relation to all-cause mortality. Metabolic health status significantly modified the association between BMI and mortality ($P$-interaction <0.001). Compared to metabolically healthy individuals with a BMI between 18.5 and 24.9 kg/m$^2$, metabolically unhealthy persons with class II/III obesity had a greater all-cause mortality risk with an adjusted HR of 1.34 (95% CI: 1.10, 1.64). This analysis was adjusted for age, sex, smoking status, alcohol drinker, disease burden, and other health-related factors. Interestingly, metabolically healthy individuals with overweight or obesity did not have a significantly greater mortality risk (overweight – adjusted HR: 0.90; 95% CI: 0.73, 1.13; class I – adjusted HR: 0.58; 95% CI: 0.42, 0.80; class II/III obesity – adjusted HR: 0.78; 95% CI: 0.48, 1.27). Varying the definition of metabolic health did not change our results substantially. In addition, we conducted multiple sensitivity analyses to address the important methodological issues that were highlighted in objective 1, but results
remained consistent. Thus, assessment of metabolic health status should be considered across all BMI classes.

There are several potential mechanisms to explain the striking differences in all-cause mortality risk between metabolically healthy and unhealthy groups. One hypothesis is that metabolic healthy and unhealthy individuals may have different postprandial metabolic adaptability. Badoub et al. compared postprandial responses after a high caloric Western meal among 35 adults (35 to 70 years), who were categorized into three groups: metabolically healthy obese, metabolically unhealthy obese, and also lean healthy individuals. Metabolically healthy obese participants exhibited better insulinemic and glycemic postprandial controls than metabolically unhealthy obese adults, and no differences in those measures when compared with metabolically healthy lean participants (8). Fabbrini et al. further investigated this concept with a longer follow-up (around two months) and tested whether metabolically normal obese individuals, defined by intrahepatic triglyceride content and insulin sensitivity, were protected against unfavorable metabolic effects of weight gain compared with metabolically abnormal obese persons who were matched for baseline BMI and fat mass (9). While body weight and fat mass gains were similar in both groups, only metabolically abnormal obese individuals exhibited decreased insulin sensitivity in adipose, skeletal muscle, and hepatic tissues, and increased very low density lipoprotein apolipoprotein B100 concentrations and secretion rates. Goodpaster et al. reported metabolically unhealthy individuals may have less favorable abdominal fat distribution across BMI groups (10). Compared to metabolically healthy persons, those with metabolic syndrome had higher visceral adipose tissue, resulting in greater levels of pro-inflammatory cytokines that may
promote insulin resistance and increase future mortality risk (10). Adiponectin levels also differed between metabolically healthy and unhealthy individuals in both non-obese and obese persons (11). Genetic predisposition may also play a crucial role. A meta-analysis identified a potential link between genetic variation near the insulin receptor substrate-1 gene and inferior metabolic status (12).

Chapter 5 addressed objective 3, using conditional inference tree analysis – a data mining approach – to construct a risk stratification algorithm for risk of developing functional decline, based on BMI and other potential risk factors. For comparison, we also analyzed the data with multivariate stepwise logistic regression. Both methods identified higher BMI, age, and comorbidity as significant risk factors for functional decline. Based on these three risk factors, conditional inference tree analysis further stratified individuals into four risk groups: 1) low risk: age ≤75.7 and modified Charlson Index =0 (6.4% of participants developed functional limitation); 2) intermediate risk I: age ≤75.7, modified Charlson Index >0, and BMI ≤38.5 (10.2% functional limitation); 3) intermediate risk II: age >75.7 (17.7% functional limitation); and 4) high risk: age ≤75.7, modified Charlson Index >0, and BMI >38.5 (38.3% functional limitation). Relative to the low risk group, all other risk groups had significantly greater risk of developing functional limitation (intermediate risk I – odds ratio (OR): 1.67; 95% CI: 1.14, 2.46; intermediate risk II – OR: 3.14; 95% CI: 2.13, 4.63; high risk – OR: 9.09; 95% CI: 4.68, 17.62).

Findings from objective 3 suggest that a data mining approach is helpful in providing an easy-to-understand data visualization of the sophisticated interactions among variables with respect to the outcome (e.g., functional decline) in the form of a
decision tree. In our study, conditional inference tree analysis generated a reliable risk stratification algorithm for developing functional limitation using health and clinical laboratory data that were extracted from the electronic medical record (EMR).

Approximately 11.3% of the GRAS cohort developed functional limitation but this percentage differed by nearly 6-fold (i.e., from low risk group: 6.4% to high risk group: 38.3%) based on three significant risk factors – age, modified Charlson Index, and BMI. Our results also further confirm the added value of BMI in the context of predicting future functional decline. This is consistent with the findings observed by Al Snih et al. that were highlighted for objective 1 (7). Excess adiposity is related to higher risk of several conditions, such as osteoarthritis of the knees and reduced muscle strength (i.e., in those with sarcopenic obesity), which may adversely affect functional ability (13–18). Furthermore, other studies have found BMI to be an independent risk factor for functional limitation (7, 19–24). Therefore, it is crucial to also consider the associations of elevated BMI with risks for other chronic medical conditions and for functional decline, when considering any possible mortality benefits.

Chapter 6 addressed objective 4, performing a meta-analysis of observational cohort studies to examine current literature on the association between weight change (weight loss, weight gain, and weight fluctuation) and all-cause mortality among community-dwelling adults aged 60 years or older. Based on the 17 studies that met the inclusion criteria, weight change was associated with greater all-cause mortality risk. The pooled relative risk (RR) for weight loss, weight gain, and weight fluctuation were 1.67 (95% CI: 1.51, 1.85; \( P < 0.001 \) for heterogeneity), 1.21 (95% CI: 1.09, 1.33; \( P = 0.03 \) for heterogeneity), and 1.53 (95% CI: 1.36, 1.72; \( P = 0.43 \) for heterogeneity), respectively.
Interestingly, study characteristics, such as average baseline age, follow-up length, geographical region, and sex, did not have statistically significant effects on the pooled RR, except for study quality on weight loss.

Results from this meta-analysis are consistent with previous findings. Systematic reviews and meta-analyses that included both middle-aged and older adults also reported higher all-cause mortality risk associated with weight loss (25–27). Our subgroup analysis revealed that weight loss may be more harmful for shorter-term mortality (≤6 years – pooled RR: 1.91; 95% CI: 1.52, 2.40; \( P \)-difference: 0.07), potentially reflecting underlying illness. However, studies with longer follow-up period (>6 years) also had a significant pooled RR of 1.56 (95% CI: 1.45, 1.67). Similarly, previous studies have observed greater all-cause mortality risk associated with weight gain, particularly excessive weight gain. Andres et al. reported highest mortality rates in adults (aged 20 to 99 at baseline) with severe weight gain (27). Excessive weight gain usually increases the risk of developing chronic diseases, such as diabetes and cardiovascular diseases, which may contribute to greater all-cause mortality risk. Lastly, Lee et al. found that older individuals with weight fluctuation did not regain the lean mass that was lost during the weight loss period in the subsequent weight regain period, which may contribute to the higher mortality risk observed in this weight change group (28).
LIMITATIONS

There are several limitations to our studies. The majority of our GRAS participants were Caucasians (i.e., non-Hispanic whites) who resided in northeastern and central Pennsylvania. Thus, our results may not be generalizable to other populations of older persons. However, studies with more diverse groups of older adults have reported similar patterns (7,29–33). Al Snih et al. (7) studied 12,725 individuals (8359 non-Hispanic white Americans, 1931 African Americans, and 2435 Mexican Americans) aged 65 years or older (mean age 73 years) over a 7-year follow-up period. Relative to those with a BMI between 18.5 and 24.9 kg/m², participants with overweight or class I obesity had lower all-cause mortality risk (overweight – HR: 0.78; 95% CI: 0.72, 0.85; class I obesity – HR: 0.80; 95% CI: 0.72, 0.90) (7). These results were adjusted for age, sex, race/ethnicity, education level, marital status, smoking status, comorbidity, and study location (7). Similar findings also were noted among studies with participants who lived outside of the United States. The Personnes Agees QUID study included 3,646 older French adults aged 65 years or older (mean age 75 years) with a 13-year follow-up (34). Relative to those with a BMI between 22 and 24.9 kg/m², individuals with a BMI between 25 and 29.9 kg/m² (adjusted HR: 0.98; 95% CI: 0.88, 1.10) or ≥30 kg/m² (adjusted HR: 1.06; 95% CI: 0.89, 1.27) did not have a significantly higher all-cause mortality risk (34). Furthermore, consistent patterns were noted among other studies in Europe (35), Australia (36,37), South America (38), and Asia (39,40). Our findings from objectives 2 and 3 also are comparable to those of other studies with more diverse populations (7,19,20,22,23,41,42).
To examine the obesity paradox, our studies used BMI as a measurement for adiposity. Having body composition and other anthropometric measurements would allow us to better discern between fat-free mass and fat mass. This would be useful because sarcopenia is common among older adults and sarcopenic obesity is associated with greater risk of functional decline and mortality (18,43–45). However, it is also important to note that most such measurements are difficult to use in a routine clinical or wellness visit and are impractical for large population studies. Previous investigations have reported an association between body composition and metabolic health status. In particular, unhealthy metabolic status is positively related to higher abdominal or visceral fat, regardless of overall adiposity (46–50). Therefore, we incorporated metabolic health status in addition to BMI to examine whether it could help differentiate overweight or mildly obese survivors from non-survivors in objective 2. However, there is a lack of consensus criteria to define “metabolically unhealthy”. Thus, more studies are warranted to establish a standard definition that would be sensitive, specific, and also feasible to apply in both clinical and public health settings.

Although most of our demographic and health information were extracted from the EMR, we relied on self-reported activities of daily living (ADL) and instrumental activities of daily living (IADL) for functional status in objective 3. However, these measures have been shown to correlate well with more objective physical performance tests (51–53). Furthermore, we did not have any physical activity data. Physical activity is related to functional limitation and all-cause mortality, independent of BMI, age, sex, disease status, and/or other sociodemographic and psychosocial factors (22,54,55).
An important limitation to our meta-analysis is that we did not account for weight change intentionality because most included studies either did not assess or incorporate this information in their analyses. It is quite difficult to reliably distinguish between self-reported volitional and non-volitional weight loss. Intentionality could play an important role in the association between weight change, especially weight loss, and all-cause mortality. Non-volitional weight loss often reflects underlying inflammatory conditions or illnesses, which may increase mortality risk (56). While it is logical to associate desirable outcomes with volitional weight loss, results have been equivocal (57–61). Shea et al. (59) investigated the association between intentional weight loss and all-cause mortality using a follow-up data from the Trial of Nonpharmacologic Intervention in the Elderly, a randomized trial that was completed in 1995. This trial included 585 overweight or obese older adults with hypertension and found that intentional dietary weight loss did not increase the risk of all-cause mortality over a course of 12 years (HR: 0.95; 95% CI: 0.56-1.61) (59). However, Wallace et al. (58) presented different findings with a sample of 229 males aged 65 years and older. The authors noted a trend for greater mortality risk among individuals who were “successful” in losing weight compared to their counterparts who attempted to lose weight but were not successful (58). In addition, relative to those with stable weight, participants who lost weight regardless of intention had higher mortality rates (58). To explain this phenomenon, Wallace et al. suggested that “weight loss, whether voluntary or involuntary, has untoward physiologic effects that can lead to increased morbidity and mortality.” (58) From a mechanistic standpoint, weight loss may be a sign of inability to maintain energy balance and is often accompanied with increased susceptibility to infection, weakened immunity, and
decreased skeletal muscle and bone mass, which may negatively impact functional ability and overall health status (58,62–66). All of these changes, along with the likelihood that older adults may have limited metabolic reserve and decreased ability to restore those reserve, could contribute to increased all-cause mortality risk (58).

Lastly, the main outcome for studies 1 and 2 was all-cause mortality instead of other health outcomes, such as cardiovascular diseases or cause-specific mortality, which may have different associations with BMI (or with the joint effects of BMI and metabolic health) (67,68). Similarly, our meta-analysis examined the association between weight change and all-cause mortality and so suffers the same limitation. Despite the elevated mortality associated with weight loss in population studies, it is important to note that weight reduction intervention studies of selected overweight or obese older persons have shown improvements in diabetes, coronary heart disease, and functional status (69).

**DIRECTIONS FOR FUTURE RESEARCH**

There are several areas of studies that would help to promote further understanding of the obesity paradox and determine whether modification of the current NIH BMI guidelines for older persons may be warranted:

1. It is crucial to validate our findings in other populations of older persons.

   Although current studies with more diverse populations have reported similar findings, it would be important to examine whether the “desirable” BMI range differs among older individuals of different backgrounds (e.g., racial/ethnic).

2. Conduct studies that could help to provide the specificity needed to develop meaningful public health and clinical guidelines. For instance, treating BMI as
a continuous variable using a restricted cubic spline approach could provide more precise estimates on the association between BMI and all-cause mortality. Moreover, performing subgroup analyses (e.g., age, sex, racial background, and disease status) could help us understand if or how this association differs among individuals with different characteristics. Future research could also apply a data mining approach in addition to a traditional regression method so that complex interactions may be addressed and to enhance the translation of findings.

3. To better clarify the age range at which having excess body fat may become protective against all-cause mortality, we need longitudinal studies with multiple weight, height, and other health measurements across the lifespan – or at least from middle to old age.

4. Future studies should focus on identifying the characteristics that discern overweight and mildly obese survivors from non-survivors to better assist health professionals in detecting at-risk individuals for early treatment.

5. Further studies are needed to clarify whether overweight and mildly obese older persons with sarcopenia exhibit reduced survival advantage, as suggested by Murphy et al. (70).

6. Since body imaging techniques are the gold standard for diagnosing sarcopenia, it would be extremely helpful to identify a more feasible proxy indicator for decreased muscle mass. One example could potentially be assessment of metabolic health status; studies have showed an association between metabolic health and body composition. Specifically, unhealthy
metabolic status is associated with higher visceral fat and in persons of advanced age it will be important to discern whether they also have sarcopenia.

7. Going forward there is a clear need for standardization of criteria and terminology in relation to the definition of “metabolic health” and for “weight change”. These advances would enable future investigations to enhance comparability and provide the specificity needed to inform practice.

8. Lastly, it is crucial to also consider the associations of elevated BMI with risks for other chronic medical conditions and for functional decline, when considering any possible mortality benefits. Quality of life and independent functioning may be more important than longevity.

In conclusion, findings presented in this dissertation contribute to the obesity paradox literature. Our results have further substantiated the obesity paradox concept among older persons. Methodological issues could not fully explain this phenomenon. Furthermore, our findings suggest that the obesity paradox may be partially explained by the inclusion of metabolically healthy overweight and obese older persons, who do not have elevated mortality risk, in population studies of BMI and mortality. Therefore, future studies should focus on identifying the characteristics that discern overweight and mildly obese survivors from non-survivors to better assist health professionals in detecting at-risk individuals for early treatment.
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