DIABETES, CARDIOVASCULAR DISEASE, AND MORTALITY IN RELATION TO WEIGHT PATTERNS DURING MIDDLE AGE CHARACTERIZED BY FUNCTIONAL PRINCIPAL COMPONENTS ANALYSIS

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A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN THE DIVISION OF BIOLOGY AND MEDICINE AT BROWN UNIVERSITY

PROVIDENCE, RHODE ISLAND

MAY 2009
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ABSTRACTS


**NATIONAL PRESENTATIONS**


**LOCAL PRESENTATIONS**


PREFACE

A dissertation in the Department of Community Health takes the form of three publishable papers (Chapters 2 through 4). This document was reformatted to comply with the requirements of the Graduate School at Brown University.

The Framingham Heart Study – Cohort (FHS-C) is conducted and supported by the NHLBI in collaboration with the FHS-C Study Investigators. This dissertation was prepared using a limited-access dataset obtained from the NHLBI and does not necessarily reflect the opinions or views of the FHS-C or the NHLBI. We acknowledge the enormous contributions of the FHS Study Investigators, study staff, and participants in creating and maintaining this dataset.
ACKNOWLEDGEMENTS

I would like to acknowledge and thank my dissertation committee, Kate Lapane, Chuck Eaton, and Tom Lasater, for their guidance, feedback, and patience during the dissertation process. I would also like to thank Chuck for being my research advisor and mentor. Working with Chuck I have felt like a junior colleague and a member of the team, and I appreciate the encouragement and space to grow as a researcher. I would also like to thank Kate for being my teacher, mentor, and role model. Kate has taught me much about epidemiology, research, collaboration, teaching, and life. I aspire to be as exceptional a mentor to future students as Kate has been to me.

I would like to acknowledge and thank the network of family, friends, and colleagues who supported and encouraged me over the past four years. I’d like to thank the “epi-punks” for studying and commiserating with me and the folks at the CPCP for providing me with a professional home. I’d like to thank my friends, both near and far, for distracting me and cheering me on. I’d like to thank my family for their love and support and faith, especially my mother Cynthia Waring and my brother Nathaniel Waring. Finally, I’d like to thank my best friend and fiancé, Ben FrantzDale, for being my “technical, spiritual, and menu advisor” as well as always believing in me.
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CHAPTER 1: INTRODUCTION
Currently, one third of adults in the United States are overweight and one third are obese.\textsuperscript{1} The increased morbidity and mortality associated with overweight and obesity, weight gain, and weight fluctuations are well documented.\textsuperscript{2-37} Weight history provides information about disease risk beyond current weight,\textsuperscript{4-7,16,38} and the effect of weight variability on cardiovascular risk and mortality may differ across categories of baseline weight.\textsuperscript{18,36,39} Yet many studies assess weight at only one or a limited number of time points.\textsuperscript{4-10,12,25-34,40-42}

Although there is strong clinical trial evidence that modest weight loss can delay or prevent the development of diabetes, hypertension, and dyslipidemia among overweight and mildly obese adults,\textsuperscript{12,43-50} many adults are unable to maintain weight losses.\textsuperscript{51,52} Given the negative health consequences of obesity and the limited long-term effectiveness of weight loss programs, efforts to prevent weight gain in adults is essential to preventing the health effects of overweight and obesity.\textsuperscript{53,54} However, strategies to prevent weight gain necessarily differ for different weight trajectories across adulthood. For example, an intervention aimed at preventing a gradual increase in weight would differ from an intervention aimed at preventing repeated gains and losses. Characterizing weight trajectories across adulthood and linking these weight patterns to increased morbidity and mortality can inform the development of intervention efforts targeted at particular trajectories deleterious to health.

Methods that capture the time-varying and lifelong nature of weight trajectories are needed to better understand how weight impacts health. Functional data methods may provide better characterizations of weight trajectories. In functional data analysis, a person’s history is considered as a single datum, rather than a set of repeated measures. In
this dissertation, we characterized weight patterns during middle age using functional principal components analysis, evaluated correlates of these weight patterns, and quantified the association between overall weight status and weight cycling during middle age and incident diabetes, cardiovascular events, and mortality.
CHAPTER 2: CORRELATES OF WEIGHT PATTERNS DURING MIDDLE AGE
CHARACTERIZED BY FUNCTIONAL PRINCIPAL COMPONENTS ANALYSIS
Abstract

Background: Overweight, obesity, weight gain, and weight cycling are associated with increased health risk. Characterizing weight trajectories using functional data methods may further our understanding of how weight impacts health. We characterize weight patterns during middle age using functional principal components analysis and describe correlates of these weight patterns.

Methods: Using the subset of the Framingham Heart Study original cohort limited-access dataset (n = 1,429), we conducted a functional principal components analysis of body mass index from 40 to 55 years. Scores from the principal component functions defined weight patterns. Gender-specific logistic regression models provided estimates of the association between sociodemographic and lifestyle factors and the weight patterns.

Results: The principal component functions described weight trajectories during middle age as overall weight status, weight changes, and weight cycling. Being overweight or obese at age 25 years was the most consistent correlate of weight patterns during middle age (for men and women, adjusted ORs = 14.2, 3.7 for overall overweight and 99.5, 28.3 for overall obese; 2.7 for weight loss among women; 1.4, 3.9 for weight cycling). Weight status at 25 years was not associated with weight loss during middle age in men or weight gains in either gender.

Conclusions: Functional principal components analysis described weight patterns during middle age. The strong associations between weight status at age 25 years and overall weight status and weight cycling during middle age underscore the importance of addressing overweight and obesity earlier in life.
Introduction

The increases in morbidity and mortality associated with overweight and obesity, weight gain, and weight fluctuations are well documented. While there is strong clinical trial evidence that modest weight loss can delay or prevent the development of diabetes, hypertension, and dyslipidemia among overweight and mildly obese adults, many adults are unable to maintain weight losses. The timing and duration of overweight/obesity may be important for explaining health risk, yet much of the evidence of the impact of weight during adulthood on health has come from studies that assessed weight at one or a few time points. Methods that capture the time-varying and lifelong nature of weight trajectories are needed to better understand how weight impacts health.

Functional data methods may provide better characterizations of weight trajectories. In functional data analysis, a person’s history is considered as a single datum, rather than a set of repeated measures. The purpose of this study is twofold. First, we sought to characterize weight patterns during middle age using functional principal components analysis. Second, we evaluated correlates of these weight patterns.

Methods

– Dataset and participants–

The Brown University IRB approved this study. We used the limited-access dataset of the Framingham Heart Study (FHS) Original Cohort. The design of the FHS has been described in detail elsewhere. Briefly, in 1948 – 1952, researchers enrolled 5,209 men and women aged 28 to 62 years without clinically apparent cardiovascular
disease. Biennial study exams included an interview, clinical examination, and laboratory tests. Of the 5,079 participants who provided informed consent for inclusion in the limited-access dataset, we excluded participants who were enrolled in the FHS cohort after the age of 40 years (n = 3071), those who did not attend FHS exams after age 55 years (n = 332), and those missing BMI measurements for more than four consecutive years or at two or more exams during this period (n = 247), resulting in a sample of 1,429 adults for the characterization of weight patterns.

- Characterizing weight patterns -

We operationalize weight patterns during middle age using principal component scores derived from a functional principal components analysis of body mass index (BMI) from age 40 to 55 years. The limited-access FHS dataset included exact BMI for the majority of participant assessments. Because weight was provided in the limited-access dataset in 5-pound groupings to preserve participant confidentiality, we used a randomly selected weight from this range and proximally measured height to calculate BMI at the minority of exams for which exact BMI was not provided. Because conceptually measured weights represent an underlying continuous biological process, we linearly interpolated BMI for intervening ages using the two nearest observed BMIs for up to a 4-year window and then converted BMI from 40 to 55 years to functional form using a linear combination of cubic B-spline basis functions. These trajectories were based on an average of 8 BMI observations per participant.

The theory and methodology of functional principal components analysis (PCA) have been described in detail elsewhere. Briefly, this approach applies traditional
principal components methodology to determine the most important ways each trajectory varies from the average trajectory. Each subsequent principal component (PC) function explains some variability that is not already explained by the previously defined PC functions. We visualized the results of the functional PCA by graphing the mean trajectory with the addition and subtraction of two standard deviations of each PC function. Scores for each participant for each PC function reflect the extent to which the participant’s trajectory resembles that PC function. We divided the scores into weight patterns based on interpretability.

- Correlates -

We considered sociodemographic variables and health behaviors as correlates of weight patterns during middle age. At the first exam, participants reported their educational attainment and weight at age 25 years. Recalled weight at age 25 years was provided in 5-pound groupings in the limited-access dataset to preserve confidentiality. For the majority of participants, both their minimum and maximum possible BMI calculated from measured height at exam 1 were either in the overweight/obese (25 kg/m² ≤ BMI) or underweight/normal weight range (BMI < 25 kg/m²). For the 100 participants whose possible BMI range included 25 kg/m², we randomly selected a weight from the 5-pound range provided and categorized their weight status at age 25 years based on this weight. For four characteristics that might vary during middle age, we used the closest assessment to age 40 years in order to capture the level of the characteristic that might influence the development of the weight patterns. Current smokers included those who reported smoking cigarettes, pipes, and/or cigars since the previous FHS exam. Moderate
alcohol consumption of up to one drink per day for women and two drinks per day for men has been shown to have health benefits. Alcohol was provided in the FHS limited-access dataset as ounces per week or month or number of various types of alcoholic drinks per week. We converted these data into average grams of ethanol consumed per day and categorized daily alcohol consumption as none, moderate consumption (up to 15/30 grams per day for women/men), or heavier consumption (more than 15/30 grams per day for women/men). After exam 1, martial status was not assessed until exam 10 (when participants were aged 48 – 60 years). Because neither divorce nor separation was common, we categorized marital status at exam 1 as married, widowed, or single/divorced/separated.

- Statistical analyses -

There is evidence men may underestimate their weight status and that women may overestimate their weight status. Women are more likely to report attempting to lose weight and self-reported weight control practices differ by gender. Women experience menopause during middle age, which may put them at increased risk for weight gain. Therefore, the correlates of weight patterns during middle age may differ by gender. Functional PCA for men and women separately resulted in qualitatively identical PC functions but the mean trajectories differed slightly by gender. We elected to characterize weight patterns using functional PCA for men and women together, but to examine correlates of weight patterns stratified by gender.

The analysis of correlates excluded 30 participants who were missing one or more covariates and 14 participants who were consistently underweight, resulting in a sample
size of 1,385 adults (615 men and 770 women). We compared the prevalence of each weight pattern in relation to gender using chi-square tests. We used logistic regression models to identify crude and multivariable correlates of each weight pattern. For the overall weight status and changes we used polytomous logistic regression models. In polytomous logistic regression the outcome takes one of three or more categories and models are simultaneously fit using maximum likelihood to estimate odds ratios for each group compared to a common reference group.\textsuperscript{61, pp. 608-618} Variables were added to the model one at a time, in order of the largest crude relationship. The most informative model for each weight pattern was chosen after considering the odds ratios (ORs) and 95% confidence intervals (CIs) associated with each variable and the AIC for the model. Analyses were conducted in SAS (Version 9.1.3, SAS Institute, Inc., Cary, NC) and R (www.r-project.org).

Results

Overall, participants’ mean BMI was 25.1 kg/m\(^2\) (SD = 3.9 kg/m\(^2\)) at age 40 years and increased to a mean of 26.3 kg/m\(^2\) (SD = 4.3 kg/m\(^2\)) at age 55 years (Figure 2.1). The first PC function reflects differences in overall weight status and explained the majority of the variation in BMI from 40 to 55 years (Figure 2.1). Participants with high scores were heavier than average and participants with low scores were lighter than average, regardless of the shape of their BMI trajectory. Guided by standard BMI cutoffs for overweight and obesity,\textsuperscript{62} we categorized participants as normal weight (PC function 1 scores in deciles 1 – 5), overweight (deciles 6 – 9), and obese (decile 10). Median (inter-quartile range) mean BMI values across 40 to 55 years for these three groups were 22.9
kg/m$^2$ (21.7 to 24.0 kg/m$^2$) for overall normal weight (excluding 14 participants who were consistently underweight), 27.2 kg/m$^2$ (26.1 to 28.6 kg/m$^2$) for overall overweight, and 33.0 kg/m$^2$ (31.9 to 34.8 kg/m$^2$) for overall obese trajectories.

The second PC function reflects weight changes (Figure 2.1). We classified participants as experiencing a loss, neither weight loss nor weight gain, slight gain, moderate gain, or larger weight gain (quintiles of PC function 2 scores). Median (interquartile range) differences between BMI at age 55 years and BMI at 40 years for these groups were -1.2 kg/m$^2$ (-2.1 to -0.3 kg/m$^2$) for weight loss, 0.3 kg/m$^2$ (-0.5 to 0.9 kg/m$^2$) for neither weight loss nor weight gain, 1.1 kg/m$^2$ (0.4 to 1.8 kg/m$^2$) for slight weight gain, 1.8 kg/m$^2$ (1.0 to 2.6 kg/m$^2$) for moderate weight gain, and 3.6 kg/m$^2$ (2.6 to 4.6 kg/m$^2$) for larger weight gain.

PC functions 3 through 9 reflect weight cycling at increasing frequency (Figure 2.1). Participants with both high and low scores on these PCs exhibited weight cycling during middle age and participants with mid-range scores had flatter trajectories. We considered participants with a score in the highest or lowest 10% on PC functions 3 through 6 and/or in the highest or lowest 5% on PC functions 7 through 9 to be cyclers. This reflects cycling of approximately one kg/m$^2$ or more.

Weight patterns during middle age differed by gender (Figure 2.2). While similar percentages of men and women had overall obese trajectories, men were more likely to have overall overweight trajectories and women were more likely to be of normal weight ($p < 0.0001$). Men were more likely to experience weight losses and slight weight gains while women were more likely to experience larger weight gains ($p < 0.0001$). Women were more likely to experience weight cycling than men (61% versus 51%; $p = 0.003$).
Gender-specific correlates of the weight patterns are shown in the Tables. Being overweight or obese at age 25 years was strongly associated with overall overweight and overall obese trajectories among both men and women (Table 2.1). The association of overweight or obesity during young adulthood was stronger for obesity for both genders, and the association was stronger for men than for women. Lower levels of education were strongly associated with overall weight status among women but not among men. Smoking at age 40 years was protective of overall overweight and obesity among women. Overweight or obesity at age 25 years was associated with higher odds of weight loss among women but was not associated with weight loss among men or weight gains in either gender (Tables 2.2 and 2.3). While men who smoked had increased odds of both weight loss and weight gain during middle age, current smoking was not associated with weight changes in women. Overweight or obesity at age 25 years and lower levels of education were both positively associated with weight cycling in both men and women (Table 2.4). Men who smoked at age 40 years were more likely to experience weight cycling during middle age but smoking was not associated with cycling in women.

Discussion

We characterized weight patterns during middle age using functional principal components analysis (PCA). Our operationalization of weight patterns during middle age is novel and extends previous research of weight using the FHS original cohort.\(^2,6,11\) Functional PCA captures variation in individuals’ entire weight history over the period under study,\(^57\) thus allowing us to characterize weight as a time-varying and cumulative exposure. While functional data methods have been used to investigate issues of human
to our knowledge this study is the first to apply functional principal components methodology to the study of weight during adulthood.

Our findings confirm and extend previous research on weight during middle age. In our sample, mean BMI increased 1.2 kg/m$^2$ from 40 to 55 years. Weight gain during middle age is common and weight change varies among individuals.\(^8,9,52,67\) Overweight or obesity at age 25 years\(^7\) and lower levels of education\(^68\) are risk factors for overweight and obesity during middle age. Current smoking was not associated with overall weight status among men, but women who smoked were less likely to have an overall overweight or obese weight pattern. Smokers tend to weigh less than non-smokers.\(^68,69\)

Smoking cessation has been associated with weight gain and there is some evidence that women gain more weight than men.\(^69\) It is possible that the observed gender differences in the association between smoking at age 40 years and weight changes during middle age can be explained by gender differences in smoking cessation over this time period.

Previous studies have shown no difference in average weight change from 40 to 55 years in men and women in relation to BMI at age 25 years.\(^7\) While weight status at 25 years was not associated with weight gains in either gender or weight loss among men, we found that women who were overweight or obese at age 25 years were more likely to lose weight during middle age than those who were not overweight or obese at age 25 years.

Overweight or obesity at age 25 years was also a strong correlate of weight cycling during middle age in both men and women.\(^10,70\) We found that both men and women with less education were more likely to experience weight cycling. Men who currently smoked were more likely to weight cycle, which agrees with previous findings that men who
cycled were less likely to be never smokers. Current smoking as not associated with weight cycling in women in our study.

The most consistent correlate of weight patterns during middle age was weight status at age 25 years. Our findings agree with previous findings of the high correlation between BMI at age 25 years and during middle age among both men and women. Overweight or obesity during childhood or adolescence increases the likelihood of being overweight or obese as an adult obesity during childhood and adolescence has a negative impact on adult health. Our results underscore the importance of addressing overweight and obesity among children, adolescents, and young adults.

Height and weight were measured biannually according to standardized protocols, thus avoiding some of the known biases associated with self-reported weight. While BMI does not differentiate between lean and fat mass, BMI is highly correlated with waist circumference and is similarly related to total and abdominal fat and is recommended for the classification of overweight and obesity in adults by national evidence-based clinical guidelines. While we were unable to detect weight cycles occurring between biennial FHS exams, we likely captured more frequent cycling as cycling of a lower frequency.

Our operationalization of correlates was limited by the data available in the limited-access FHS dataset. Detailed information on dietary intake was not available and physical activity was not assessed by age 40 years for 60% of our sample. Because smoking, alcohol consumption, and marital status were not assessed at every FHS exam, we used the closest measurement to age 40 years. We conducted a sensitivity analysis to explore the potential effect of misreporting of weight at age 25 years. To account for
biases in self-reported and recalled weights, we also categorized weight status at age 25 years after adjusting the recalled weights by the average amounts mis-.recalled reported by Perry et al. (1995)\textsuperscript{74} stratified by gender and weight status at first examination. Categorization of weight status at 25 years after adjustment for potential bias in mis-recalled weight agreed with our initial categorization for 95\% of participants. We found that the resulting gender-specific associations were very similar to the results from our main analyses, although the odds ratios for overall weight status were modestly higher for both overall overweight and overall obesity (data not shown). These results indicate that misclassification of weight status at 25 years is unlikely to explain our results.

Information about current or previous pregnancies in the FHS limited-access dataset is limited. We included 17 women who reported pregnancy after age 40 years and it is likely that other pregnancies occurred during the study period. Weight changes surrounding pregnancy may contribute to long-term obesity\textsuperscript{77} and women with higher parity may be at increased risk for overweight and weight gain during adulthood.\textsuperscript{78} Functional data methods may be useful for characterizing weight changes surrounding pregnancy.

About 10\% of the sample had an overall obese trajectory, yet currently a third of U.S. adults are obese\textsuperscript{1}, indicating that characterization of weight patterns among heavier, contemporary cohorts may be useful in investigating the cumulative effects of weight during middle age on morbidity and mortality. Additionally, the prevalence of overweight and obesity differ racial/ethnic groups in the United States\textsuperscript{1} and the relationship between weight status and morbidity and mortality may differ among racial/ethnic groups\textsuperscript{28}, suggesting that the development of weight patterns during
adulthood and potential interventions regarding weight status and weight changes during adulthood may differ among racial/ethnic groups. Analyses of more diverse cohorts are needed to confirm our findings.

Functional principal components analysis characterized weight patterns during middle age as overall weight status, weight changes, and weight cycling. The most consistent correlate of weight patterns during middle age was weight status at 25 years, underscoring the importance of addressing overweight and obesity among children, adolescents, and young adults. Functional data methods may be useful for describing weight patterns during other life periods and for illuminating risk of morbidity and mortality associated with particular weight trajectories.
Tables and Figures

Figure 2.1: Functional principal components of BMI trajectories during middle age, with percentage of variability in BMI trajectory that each PC function represents (n = 1,429)

Lines show the effect of adding (black dashed) or subtracting (grey solid) two standard deviations from the mean BMI curve (black solid)
Figure 2.2: Gender differences in weight patterns during middle age

* Percentages may not sum to 100% due to rounding. Light grey bars represent men (n = 615) and dark grey bars represent women (n = 770).
Table 2.1: Correlates of overall weight status, by gender (OR (95% CI))*

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall overweight</td>
<td>Overall obese</td>
</tr>
<tr>
<td></td>
<td>(n = 346)</td>
<td>(n = 66)</td>
</tr>
<tr>
<td><strong>Crude</strong></td>
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<td></td>
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<tr>
<td>Education**</td>
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<tr>
<td>Less than HS</td>
<td>1.1 (0.7 – 1.7)</td>
<td>1.9 (0.9 – 3.8)</td>
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<tr>
<td>Completed HS</td>
<td>0.9 (0.6 – 1.4)</td>
<td>1.7 (0.9 – 3.4)</td>
</tr>
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<td>More than HS</td>
<td>(Referent)</td>
<td>(Referent)</td>
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<td>Not married</td>
<td>0.9 (0.4 – 1.9)</td>
<td>2.1 (0.8 – 5.1)</td>
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<td>Currently smokes</td>
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<td>0.8 (0.4 – 1.4)</td>
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<td>Daily alcohol</td>
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</tr>
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<tr>
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<td>0.8 (0.5 – 1.3)</td>
<td>0.7 (0.3 – 1.5)</td>
</tr>
<tr>
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<td>(Referent)</td>
<td>(Referent)</td>
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<tr>
<td>Heavier</td>
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<td>0.8 (0.4 – 1.5)</td>
</tr>
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<td>Overweight or obese</td>
<td>14.2 (6.8 – 29.8)</td>
<td>94.4 (38.6 – 231.2)</td>
</tr>
<tr>
<td>at age 25 years</td>
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<tr>
<td><strong>Adjusted</strong></td>
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<tr>
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</tr>
<tr>
<td>Less than HS</td>
<td>1.8 (1.1 – 2.7)</td>
<td>1.2 (0.8 – 1.8)</td>
</tr>
<tr>
<td>Completed HS</td>
<td>1.2 (0.8 – 1.8)</td>
<td>(Referent)</td>
</tr>
<tr>
<td>More than HS</td>
<td>(Referent)</td>
<td></td>
</tr>
<tr>
<td>Not married</td>
<td>1.1 (0.5 – 2.3)</td>
<td>3.2 (1.1 – 9.5)</td>
</tr>
<tr>
<td>Currently smokes</td>
<td></td>
<td>0.5 (0.3 – 0.7)</td>
</tr>
<tr>
<td>Overweight or obese</td>
<td>14.2 (6.8 – 29.9)</td>
<td>99.5 (40.4 – 245.4)</td>
</tr>
<tr>
<td>at age 25 years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Overall weight status was classified using scores from principal component (PC) function 1. Participants with scores in deciles 1 – 5 were considered overall normal weight, those with scores in deciles 6 – 9 were considered overall overweight, and those with scores in the highest decile were considered to be overall obese. Participants with an overall underweight/normal weight pattern were used as the reference group (n = 203 men, 478 women).

** HS: high school
Table 2: Correlates of weight gains or losses among men (OR (95% CI)) *

<table>
<thead>
<tr>
<th></th>
<th>Loss (n = 149)</th>
<th>Slight gain (n = 132)</th>
<th>Moderate gain (n = 110)</th>
<th>Larger gain (n = 93)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crude</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than HS</td>
<td>1.2 (0.6 – 2.2)</td>
<td>1.2 (0.6 – 2.2)</td>
<td>1.1 (0.6 – 2.1)</td>
<td>2.3 (1.2 – 4.7)</td>
</tr>
<tr>
<td>Completed HS (Referent)</td>
<td>1.3 (0.7 – 2.2)</td>
<td>1.0 (0.5 – 1.7)</td>
<td>0.6 (0.3 – 1.1)</td>
<td>1.1 (0.6 – 2.3)</td>
</tr>
<tr>
<td>More than HS (Referent)</td>
<td>1.1 (0.6 – 2.2)</td>
<td>1.0 (0.5 – 1.7)</td>
<td>0.6 (0.3 – 1.1)</td>
<td></td>
</tr>
<tr>
<td>Not married</td>
<td>1.6 (0.6 – 4.1)</td>
<td>1.1 (0.4 – 3.2)</td>
<td>1.4 (0.5 – 4.0)</td>
<td>2.4 (1.3 – 4.7)</td>
</tr>
<tr>
<td>Currently smokes</td>
<td>1.8 (1.1 – 3.2)</td>
<td>1.2 (0.7 – 2.0)</td>
<td>2.1 (1.2 – 3.9)</td>
<td>2.4 (1.3 – 4.7)</td>
</tr>
<tr>
<td>Daily alcohol consumption</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (Referent)</td>
<td>0.8 (0.4 – 1.5)</td>
<td>0.6 (0.3 – 1.3)</td>
<td>0.6 (0.3 – 1.3)</td>
<td>0.7 (0.3 – 1.6)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.0 (0.6 – 1.8)</td>
<td>0.6 (0.3 – 1.2)</td>
<td>1.0 (0.6 – 1.9)</td>
<td>1.0 (0.5 – 2.0)</td>
</tr>
<tr>
<td>Heavier</td>
<td>1.2 (0.8 – 2.0)</td>
<td>0.7 (0.4 – 1.3)</td>
<td>0.6 (0.3 – 1.1)</td>
<td>0.6 (0.3 – 1.0)</td>
</tr>
<tr>
<td>Overweight or obese at age 25 years</td>
<td>1.9 (1.1 – 3.2)</td>
<td>1.2 (0.7 – 1.9)</td>
<td>2.1 (1.2 – 3.9)</td>
<td>2.4 (1.3 – 4.6)</td>
</tr>
<tr>
<td><strong>Adjusted</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently smokes</td>
<td>1.3 (0.8 – 2.1)</td>
<td>0.7 (0.4 – 1.3)</td>
<td>0.6 (0.3 – 1.1)</td>
<td>0.6 (0.3 – 1.1)</td>
</tr>
<tr>
<td>Overweight or obese at age 25 years</td>
<td>1.3 (0.8 – 2.1)</td>
<td>0.7 (0.4 – 1.3)</td>
<td>0.6 (0.3 – 1.1)</td>
<td>0.6 (0.3 – 1.1)</td>
</tr>
</tbody>
</table>

* Weight change categories were based on scores on PC function 2. Participants with scores in the lowest quintile experienced weight losses. Participants with scores in the second quintile had fairly flat BMI trajectories from 40 to 55 years. Participants with scores in the third, fourth, and highest quintiles experienced weight gains of increasing magnitude during middle age. Participants experiencing neither losses nor gains were used as the reference group (n = 131 men).

** HS: high school
Table 2.3: Correlates of weight gains or losses among women (OR (95% CI)) *

<table>
<thead>
<tr>
<th></th>
<th>Loss (n = 121)</th>
<th>Slight gain (n = 146)</th>
<th>Moderate gain (n = 168)</th>
<th>Larger gain (n = 191)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crude</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than HS</td>
<td>1.9 (1.0 – 3.6)</td>
<td>0.8 (0.5 – 1.5)</td>
<td>1.1 (0.6 – 2.0)</td>
<td>1.1 (0.6 – 1.9)</td>
</tr>
<tr>
<td>Completed HS (Referent)</td>
<td>1.3 (0.7 – 2.4)</td>
<td>0.7 (0.4 – 1.3)</td>
<td>1.0 (0.6 – 1.7)</td>
<td>1.5 (0.9 – 2.5)</td>
</tr>
<tr>
<td>More than HS (Referent)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not married</td>
<td>1.0 (0.5 – 2.0)</td>
<td>0.9 (0.5 – 1.8)</td>
<td>0.9 (0.5 – 1.7)</td>
<td>1.3 (0.7 – 2.4)</td>
</tr>
<tr>
<td>Currently smokes</td>
<td>1.1 (0.7 – 1.8)</td>
<td>0.9 (0.6 – 1.5)</td>
<td>1.0 (0.6 – 1.5)</td>
<td>1.0 (0.7 – 1.6)</td>
</tr>
<tr>
<td>Daily alcohol consumption</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (Referent)</td>
<td>2.2 (1.2 – 3.8)</td>
<td>0.9 (0.5 – 1.6)</td>
<td>1.0 (0.6 – 1.8)</td>
<td>1.4 (0.9 – 2.4)</td>
</tr>
<tr>
<td>Moderate (Referent)</td>
<td>1.2 (0.6 – 2.4)</td>
<td>1.1 (0.6 – 1.9)</td>
<td>1.0 (0.6 – 1.9)</td>
<td>0.8 (0.4 – 1.5)</td>
</tr>
<tr>
<td>Heavier</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight or obese at age 25 years</td>
<td>2.7 (1.5 – 4.9)</td>
<td>0.6 (0.3 – 1.3)</td>
<td>0.6 (0.3 – 1.2)</td>
<td>0.8 (0.4 – 1.4)</td>
</tr>
<tr>
<td>Adjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight or obese at age 25 years</td>
<td>2.7 (1.5 – 4.9)</td>
<td>0.6 (0.3 – 1.3)</td>
<td>0.6 (0.3 – 1.2)</td>
<td>0.8 (0.4 – 1.4)</td>
</tr>
</tbody>
</table>

* Weight change categories were based on scores on PC function 2. Participants with scores in the lowest quintile experienced weight losses. Participants with scores in the second quintile had fairly flat BMI trajectories from 40 to 55 years. Participants with scores in the third, fourth, and highest quintiles experienced weight gains of increasing magnitude during middle age. Participants experiencing neither losses nor gains were used as the reference group (n = 144 women).

** HS: high school
Table 2.4: Correlates of weight cycling, by gender (OR (95% CI))*

<table>
<thead>
<tr>
<th></th>
<th>Men Cycling (n = 314)</th>
<th>Women Cycling (n = 468)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crude</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than HS</td>
<td>1.4 (0.9 – 2.1)</td>
<td>2.0 (1.3 – 2.9)</td>
</tr>
<tr>
<td>Completed HS</td>
<td>1.6 (1.1 – 2.3)</td>
<td>1.9 (1.4 – 2.8)</td>
</tr>
<tr>
<td>More than HS</td>
<td>(Referent)</td>
<td>(Referent)</td>
</tr>
<tr>
<td>Not married</td>
<td>1.1 (0.6 – 2.2)</td>
<td>1.0 (0.7 – 1.5)</td>
</tr>
<tr>
<td>Currently smokes</td>
<td>1.6 (1.1 – 2.4)</td>
<td>1.1 (0.8 – 1.4)</td>
</tr>
<tr>
<td>Daily alcohol consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0.6 (0.4 – 1.0)</td>
<td>1.3 (0.8 – 1.4)</td>
</tr>
<tr>
<td>Moderate</td>
<td>(Referent)</td>
<td>(Referent)</td>
</tr>
<tr>
<td>Heavier</td>
<td>0.9 (0.6 – 1.4)</td>
<td>0.8 (0.6 – 1.2)</td>
</tr>
<tr>
<td>Overweight or obese at age 25 years</td>
<td>1.4 (1.0 – 2.0)</td>
<td>4.2 (2.5 – 7.2)</td>
</tr>
<tr>
<td><strong>Adjusted</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than HS</td>
<td>1.4 (0.9 – 2.0)</td>
<td>1.7 (1.2 – 2.5)</td>
</tr>
<tr>
<td>Completed HS</td>
<td>1.5 (1.0 – 2.3)</td>
<td>1.8 (1.3 – 2.6)</td>
</tr>
<tr>
<td>More than HS</td>
<td>(Referent)</td>
<td>(Referent)</td>
</tr>
<tr>
<td>Currently smokes</td>
<td>1.6 (1.1 – 2.4)</td>
<td></td>
</tr>
<tr>
<td>Overweight or obese at age 25 years</td>
<td>1.4 (1.0 – 2.0)</td>
<td>3.9 (2.3 – 6.7)</td>
</tr>
</tbody>
</table>

* Participants with scores in the highest or lowest 10% on PC functions 3 – 6 and/or in the highest or lowest 5% on PC functions 7 – 9 to be cyclers. This reflects cycling of approximately one kg/m² or more. Participants who did not experience weight cycling were used as the reference group (n = 301 men, 302 women).

** HS: high school
CHAPTER 3: INCIDENT CARDIOVASCULAR DISEASE AND MORTALITY IN RELATION TO OVERALL WEIGHT STATUS AND WEIGHT CYCLING DURING MIDDLE AGE
Abstract
Background: The timing and duration of overweight and weight cycling may impact cardiovascular risk.

Objective: To quantify the effect of overall weight status and weight cycling during middle age on incident cardiovascular disease (CVD) and mortality.

Design: Prospective cohort.

Setting: Framingham, Massachusetts.

Patients: 1,429 participants from the Framingham Heart Study original cohort limited-access dataset.

Measurements: We jointly categorized overall weight status and weight cycling using scores from a functional principal components analysis of body mass index from 40 to 55 years.

Results: Compared to an overall normal weight trajectory without weight cycling, normal weight with cycling (adjusted HR = 1.5; 95% CI: 1.1 – 2.0), overweight without cycling (adjusted HR = 1.5; 95% CI: 1.1 – 2.0), overweight with cycling (adjusted HR = 1.4; 95% CI: 1.0 – 1.8), and obese trajectories (adjusted HR = 2.0; 95% CI: 1.4 – 2.9) were associated with increased rates of coronary heart disease. Associations with cerebrovascular accidents were stronger (adjusted HRs were 2.1, 2.1, 2.3, and 4.5, respectively). Results were similar for CVD. These weight patterns were also associated with CVD mortality (adjusted HRs ranged from 1.4 to 1.8). Only obesity (adjusted HR=1.4, 95% CI: 1.1 – 1.9) and overweight/cycling (adjusted HR = 1.2; 95% CI: 1.0 – 1.4) were associated with all-cause mortality.

Limitations: These findings may not be generalizable to persons of nonwhite race or ethnicity.
Conclusions: Weight cycling was associated with higher rates of cardiovascular events among adults with an overall normal weight trajectory but not among those with an overall overweight trajectory. Our findings suggest that overweight adults should attempt weight loss, even if weight losses are not maintained and that normal weight adults should avoid weight cycling.

Introduction

Overweight, obesity, and weight fluctuations during adulthood are associated with an increased risk of elevated blood pressure, adverse lipid profiles, and elevated blood glucose, which in turn are strong risk factors for atherosclerosis and cardiovascular disease (CVD). While obesity and weight changes indirectly affect the risk of CVD and mortality through blood glucose, lipids, and blood pressure, weight may also impart risk independent of these traditional CVD risk factors or through other pathways such as endothelial dysfunction or inflammation. It is important to identify weight trajectories that are associated with higher risk of CVD and mortality in adults, regardless of the mechanisms through which they act.

Weight history may provide information about cardiovascular risk beyond current weight, yet many studies assess weight at only one or a limited number of time points. Methods that capture the time-varying and cumulative weight patterns have been demonstrated in this dissertation. Previous research has suggested that the effect of weight variability on cardiovascular risk and mortality may differ across categories of baseline weight. In this paper we quantified the association between
overall weight status and weight cycling during middle age and incident cardiovascular events and mortality.

**Methods**

– Dataset and participants –

The Brown University IRB approved this study. We used the limited-access dataset of the Framingham Heart Study (FHS) Original Cohort.\textsuperscript{55} The design of the FHS has been described in detail elsewhere.\textsuperscript{56} Briefly, in 1948 – 1952, researchers enrolled 5,209 men and women aged 28 to 62 years without clinically apparent cardiovascular disease. Biennial study exams included an interview, clinical examination, and laboratory tests. Of the 5,079 participants who provided informed consent for inclusion in the limited-access dataset, we excluded participants who were enrolled in the FHS cohort after the age of 40 years (n = 3071), those who did not attend FHS exams after age 55 years (n = 332), and those missing BMI measurements for more than four consecutive years or at two or more exams during this period (n = 247), resulting in a sample of 1,429 adults for the characterization of weight patterns.

- Characterization of weight patterns -

We operationalized weight patterns during middle age using principal component scores derived from a functional principal components analysis (PCA) of body mass index (BMI) from age 40 to 55 years. While CVD develops over a number of years, weight during middle age has been linked to subsequent cardiovascular morbidity and mortality.\textsuperscript{9,29} The upper limit of this period was chosen to be 55 years because CHD is
considered premature if it occurs before age 55 years for men or before age 65 years for women. Additionally, our restriction to this age range avoids the bias in mean BMI at older ages due to the selective removal of heavier individuals from a population. The limited-access FHS dataset included BMI for the majority of participant assessments. For exams for which BMI was not provided, we used a randomly selected weight from the 5-pound range provided to preserve participant confidentiality and proximally measured height to calculate BMI. The theory and methodology of functional PCA has been described in detail elsewhere. Briefly, this approach applies traditional principal components methodology to determine the most important ways each trajectory varies from the average trajectory and participants are scored based on how similar their weight trajectory is to each mode of variation.

The first principal component (PC) function reflected differences in overall weight status. Participants with high scores were heavier than average and participants with low scores were lighter than average, regardless of the shape of their trajectory. We categorized participants’ trajectories as overall normal weight (PC function 1 score in deciles 1 – 5), overweight (deciles 6 – 9), or obese (decile 10). Median (inter-quartile range) mean BMI values across 40 to 55 years for these three groups were 22.9 kg/m$^2$ (21.7 to 24.0 kg/m$^2$) for overall normal weight (excluding 14 participants who were consistently underweight), 27.2 kg/m$^2$ (26.1 to 28.6 kg/m$^2$) for overall overweight, and 33.0 kg/m$^2$ (31.9 to 34.8 kg/m$^2$) for overall obese trajectories. The third through ninth PC functions reflect weight cycling at increasing frequency. Participants with both high and low scores on these PCs exhibit weight cycling during middle age but with gains and losses at opposite times. Scores in the highest or lowest 10% on PC functions 3 through 6
and/or in the highest or lowest 5% on PC functions 7 through 9 reflected cycling of approximately one kg/m$^2$ or more.

We jointly categorized participants by overall weight status and weight cycling. Because of the small number of participants with an overall obese weight trajectory who did not experience weight cycling ($n = 20$), we were unable to evaluate weight cycling in this group. Therefore, we classified participants as overall normal weight without cycling, overall normal weight with cycling, overweight without cycling, overweight with cycling, and overall obese.

– Cardiovascular disease and mortality –

The occurrence of cardiovascular events and mortality were ascertained using information from study exams, hospital records, death certificates, medical examiner reports, and records of private physicians and were reviewed by a panel of three FHS investigators.$^{87}$ We examined CVD subtypes separately based on evidence regarding how weight and weight cycling influences intermediate cardiovascular risk factors.$^{10,18,39,80,88}$ Coronary heart disease (CHD) events included myocardial infarction, angina pectoris, coronary insufficiency, and CHD death. Cerebral vascular accidents (CVA) included transient ischemic attacks, atherothrombotic infarctions, cerebral embolism, other CVA, and CVA death. CVD events included CHD, CVA, congestive heart failure, and other CVD death. All-cause mortality included deaths from any specific causes and from unknown causes. CHD mortality included both sudden and non-sudden deaths. CVD mortality included deaths from CHD, CVA, and other CVD.
– Potential confounders –

We considered as potential confounders variables previously found to confound the relationship between weight and the occurrence of CVD events. Three of these characteristics were not time-varying: gender, education, and weight status at 25 years. To preserve confidentiality, recalled weight at age 25 years was provided in 5-pound groupings in the limited-access dataset. For the majority of participants, both the minimum and maximum possible BMI calculated from measured height at exam 1 were either in the overweight/obese \((25 \text{ kg/m}^2 \leq \text{BMI})\) or underweight/normal weight range \((\text{BMI} < 25 \text{ kg/m}^2)\). For the 7\% \((n = 100)\) of participants whose possible BMI range included 25 kg/m\(^2\), we categorized their weight status at age 25 years based on a randomly selected weight from the 5-pound range provided. We also evaluated four time-varying potential confounders: smoking, alcohol consumption, marital status, and hormone use. We used the most recent assessment to categorize these variables at every year of age. Current smokers reported smoking cigarettes, pipes, and/or cigars since the previous FHS exam. In light of research suggesting that risk of coronary events declines after smoking cessation, \(^{89}\) we categorized participants as never smokers, current smokers, former smokers who quit within the past four years, and former smokers who quit more than four years ago. Alcohol was provided in the FHS limited-access dataset as ounces per week or month or number of various types of alcoholic drinks per week. We converted these data into average grams of ethanol consumed per day and categorized daily alcohol consumption as none, moderate (up to 15/30 grams per day for women/men), or heavier (more than 15/30) grams per day for women/men). \(^{58}\) Because neither divorce nor separation was common in the FHS cohort, we categorized marital
status as married, widowed, or single/divorced/separated. We classified women as never, recent (during the past two years), or former users of any type of hormones.

– Statistical analyses –

We excluded participants missing information on potential confounders (n = 28) and those who were consistently underweight (n = 14), resulting in a final analytic sample of 1,387 adults. We calculated the number of events and person-years for each analysis. Mortality follow-up continued from age 55 years until death or last contact with FHS investigators via telephone or in person or through the mail or as part of FHS tracking. For analyses of incident disease, follow-up continued from age 55 years until disease event, last exam attended, or time of the latest non-death event.

Kaplan-Meier estimators provided graphical comparisons of incident CVD and mortality across the various weight patterns. We estimated incidence rate ratios (IRRs) for each outcome using Cox proportional hazards models. We assessed the proportional hazards assumption visually and by examining whether there was an interaction between the measure of weight patterns and time. A priori we hypothesized that gender would be a strong confounder because of gender differences in CVD rates across adulthood and different distributions of weight patterns during middle age as found in Chapter 2 of this dissertation. Therefore, once we confirmed that gender confounded the crude estimate, we included it in the base model. Provided the inclusion of a potential confounder changed the estimated hazard ratio for a weight pattern category by at least 10%, the covariate that produced the greatest change in the IRR was retained in the model. Model building continued until the estimated IRRs were not modified by inclusion of additional
confounders. For morbidity analyses we excluded participants with documented events before age 55 years (82 participants with prevalent CHD, 9 with CVA, and 96 with CVD). Analyses were conducted in SAS (Version 9.1.3, SAS Institute, Inc., Cary, NC) and R (www.r-project.org).

**Results**

Characteristics of the sample at age 55 years in relation to weight patterns are shown in Table 3.1. Those with overall normal weight trajectories were more likely to be women and among normal weight and overweight participants, those who experienced weight cycling were more likely to be women. Overall weight status was inversely associated with education. Being overweight or obese at age 25 years was increasingly likely with increasing overall weight status. Participants with an overall obese weight pattern were more likely to abstain from alcohol and smoking.

Participants with a normal weight trajectory who experienced weight cycling and those with an overall overweight trajectory had increased rates of CHD events compared to normal weight non-cyclers, and their increased rate ratios were very similar (Table 3.2 and Figure 3.1). Participants who were obese during middle age also had increased rates of CHD. Participants with an overall normal weight trajectory who experienced weight cycling and those with an overall overweight trajectory (cyclers and those who did not experience weight cycling) had twice the rate of CVA events of normal weight non-cyclers while those with an overall obese trajectory had four and a half times the rate of CVA. Associations with CVD were similar (Table 3.2).
After adjustment for confounding, only those with an overall obese weight trajectory or those who were overweight and experienced weight cycling had increased rates of all-cause mortality (Table 3.3). Cycling among those with a normal weight trajectory, overweight, and obesity were all associated with increased rates of deaths from CVD. Results were similar for CHD mortality although there were fewer events.

Because previous research no effect of weight cycling once weight changes were accounted for, we also adjusted for weight changes (weight loss, neither weight loss nor weight gain, slight weight gain, moderate weight gain, or larger weight gain; quintiles of PC function 2 scores). Adjustment for weight changes did not alter the estimated hazards ratios (data not shown).

Discussion

We found that the effect of weight cycling on incident CVD differed by overall weight status. Among those with an overall normal weight trajectory, those who cycled had 50% higher rates of CHD and twice the rate of CVA than those whose weight did not fluctuate during middle age. However, cycling did not appear to impart additional risk among those with an overall overweight trajectory during middle age. For incident CVD, both overweight cyclers and overweight non-cyclers had increased rates compared to normal weight non-cyclers, but the estimated hazard ratios were similar. Previous research indicates that the effect of cycling on morbidity and mortality depends on underlying weight status. Weight variability has been shown to be associated with increased rate of all-cause morality and with a higher prevalence of hypertension, hypertriglyceridemia, low HDL cholesterol, and elevated fasting glucose among normal
weight, but not overweight, men. Among women with multiple cardiovascular risk factors, both obesity and weight cycling have been shown to influence serum HDL cholesterol levels.\textsuperscript{18} While weight cycling appeared to have more of a deleterious effect on HDL cholesterol levels among obese women, but the investigators did not differentiate between normal weight and overweight. The current study adds to this body of work on the effects of weight cycling on cardiovascular events and mortality.

Our findings have important implications. There is strong clinical trial evidence that modest weight loss can delay or prevent the development of diabetes, hypertension, and dyslipidemia among overweight and mildly obese adults.\textsuperscript{43,44} However, many people are unable to maintain weight losses.\textsuperscript{44,51,52,93} Current practice guidelines recommend that adult patients in primary care be screened for overweight and obesity,\textsuperscript{62,94} but these guidelines may recommend more intensive counseling than is feasible in the context of a primary care visit and some primary care providers may feel discouraged by a lack of patient motivation.\textsuperscript{95} Our results suggest that overweight adults should attempt weight loss and although individuals should strive to maintain their losses, regain and subsequent weight loss attempts may not negatively impact their cardiovascular health.

Our results also suggest that adults of normal weight should strive to maintain their current weight and should avoid weight cycling. National guidelines recommend that primary care providers assess weight status using BMI in adults at least every two years.\textsuperscript{62} For adults who are not overweight or obese, it is recommended that physicians provide education and reinforcement about weight management and encourage patients to maintain their weight. However, our findings suggest that merely maintaining weight within the normal weight range may not be sufficient to avoid CVD. More research is
needed to evaluate the health effects of weight fluctuations among normal weight individuals in order to better understand the health effects of cycling among these individuals.

Our findings add to the body of evidence linking overweight and obesity during adulthood to CVD and mortality.\textsuperscript{3,96,97} However, while many previous studies only used one or a few weight assessments,\textsuperscript{6,29,33,34} we show an effect of weight over sixteen years during middle age on subsequent CVD and mortality using a functional approach to capturing weight trajectories. We examine weight patterns in a middle-aged cohort, focus on the overall effect on CVD and mortality, and control for confounding by smoking, thus addressing three major sources of bias in many studies of body weight and mortality.\textsuperscript{96} Additionally, in this study we examine the effects of weight cycling at different weights. While previous findings indicate no effect of weight cycling after adjustment for BMI,\textsuperscript{10,80} our approach allows us to consider the effect of weight cycling within the normal weight and overweight ranges. Other studies have found an effect of weight cycling after adjusting for weight status.\textsuperscript{9,11} Our findings that normal weight individuals who experience weight cycling have increased rates of CVD and mortality similar to the increased rates of overweight non-cyclers indicates that weight cycling should be considered when selecting a reference group in studies of the impact of weight on CVD and mortality. The mixed evidence regarding the health risks associated with overweight may be explained by the inclusion of normal weight cyclers in the reference group.

Functional PCA captures variation in individuals’ entire weight history over the period under study,\textsuperscript{57} thus allowing us to characterize weight as a time-varying and
cumulative exposure. While we were unable to detect weight cycles occurring between biennial FHS exams, more frequent cycling was likely captured as cycling of a different frequency.\textsuperscript{76, pp. 52-53}

Height and weight were measured biannually according to standardized protocols, thus avoiding some of the known biases associated with self-reported weight.\textsuperscript{74} While BMI does not differentiate between lean and fat mass, BMI is highly correlated with waist circumference and is similarly related to total and abdominal fat\textsuperscript{75} and is recommended for the classification of overweight and obesity in adults by national evidence-based clinical guidelines.\textsuperscript{62,94}

The FHS was designed to study the natural history of CVD and events were reviewed by a panel of three FHS investigators using standardized criteria for each type of event.\textsuperscript{98} The validity of the ascertainment of CVD events is a major strength of this study. Atherosclerosis develops over years or decades and the long follow-up of the FHS is another strength of this study.

There is potential for unmeasured and residual confounding in the present study. While marital status, smoking, alcohol consumption, and hormone use were assessed regularly, we could not update these variables between exams or after the last exam attended, potentially resulting in misclassification at the time of the acute event. To assess the potential impact of error in recalled weight at age 25 years, we also classified weight status at 25 years after adjusting BMI by the average number of pounds recalled for groups defined by gender and weight status at the time of recall.\textsuperscript{74} We found that adjusted models using this variable resulted in very similar estimated hazards ratios for all six outcomes in relation to overall weight status and weight cycling (data not shown).
The sample was fairly lean (average BMIs at 40 and 55 years were 25.1 kg/m$^2$ and 26.3 kg/m$^2$, respectively) and only 10% of the sample had an overall obese trajectory. Due to the relatively small number of adults with an overall obese trajectory, we were unable to separate adults who experienced weight cycling ($n = 113$) from those that did not ($n = 20$). Currently one third of U.S. adults are obese including 5% who are extremely obese, and research examining the effects of cycling on disease risk across increasing levels of obesity is needed. Although major findings from this cohort have been found to be valid for more contemporary cohorts and cohorts composed of more racially/ethnically diverse individuals, the prevalence of overweight and obesity differs among racial/ethnic groups in the United States. Moreover, the relationship between weight status and morbidity and mortality may differ among racial/ethnic groups, suggesting that the association between weight patterns during middle age and CVD and mortality may differ among racial/ethnic groups. Since functional principal components analysis has proved useful for characterizing weight patterns and linking these patterns with later disease, future research could use this analytic technique to examine weight patterns during other important life periods – such as pregnancy or childhood – and the development of subsequent morbidity and mortality.

Our findings suggest that adults of normal weight should strive to maintain their weight and avoid weight cycling. Our results also suggest that overweight adults should attempt weight loss without concern that weight regain and subsequent weight loss attempts will increase their risk of CVD and death. Given the high prevalence of overweight and obesity among adults, children, and adolescents and links between childhood obesity and morbidity and mortality during adulthood understanding the
relationship of weight status and weight changes on risk of subsequent morbidity and mortality will only become more important to the primary prevention of CVD in the future.
### Tables and Figures

Table 3.1: Characteristics of the sample at age 55 years in relation to overall weight status and weight cycling during middle age (n = 1,387), %

<table>
<thead>
<tr>
<th></th>
<th>Normal weight No cycling</th>
<th>Normal weight Cycling</th>
<th>Overweight No cycling</th>
<th>Overweight Cycling</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>358</td>
<td>324</td>
<td>227</td>
<td>345</td>
<td>133</td>
</tr>
<tr>
<td>Female</td>
<td>68.4</td>
<td>72.2</td>
<td>22.9</td>
<td>50.1</td>
<td>50.4</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>24.9</td>
<td>26.5</td>
<td>31.7</td>
<td>35.1</td>
<td>35.4</td>
</tr>
<tr>
<td>Completed high school</td>
<td>37.7</td>
<td>42.9</td>
<td>29.5</td>
<td>42.3</td>
<td>47.4</td>
</tr>
<tr>
<td>More than high school</td>
<td>37.4</td>
<td>30.6</td>
<td>38.8</td>
<td>22.6</td>
<td>17.3</td>
</tr>
<tr>
<td>Overweight or obese at age 25 years</td>
<td>4.2</td>
<td>6.8</td>
<td>30.4</td>
<td>30.4</td>
<td>74.4</td>
</tr>
<tr>
<td>Marital status *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>84.6</td>
<td>79.0</td>
<td>89.4</td>
<td>87.0</td>
<td>82.0</td>
</tr>
<tr>
<td>Widowed</td>
<td>5.3</td>
<td>9.3</td>
<td>3.1</td>
<td>3.5</td>
<td>8.3</td>
</tr>
<tr>
<td>Single/divorced/separated</td>
<td>9.8</td>
<td>10.3</td>
<td>7.1</td>
<td>8.4</td>
<td>9.8</td>
</tr>
<tr>
<td>Smoking status *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>28.2</td>
<td>21.6</td>
<td>22.5</td>
<td>29.0</td>
<td>36.1</td>
</tr>
<tr>
<td>Current</td>
<td>51.4</td>
<td>56.2</td>
<td>46.7</td>
<td>47.8</td>
<td>43.6</td>
</tr>
<tr>
<td>Quit &lt;= 4 years ago</td>
<td>6.2</td>
<td>5.6</td>
<td>8.4</td>
<td>4.6</td>
<td>4.5</td>
</tr>
<tr>
<td>Quit &gt; 4 years ago</td>
<td>14.3</td>
<td>16.7</td>
<td>22.5</td>
<td>18.6</td>
<td>15.8</td>
</tr>
<tr>
<td>Daily alcohol consumption *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>19.3</td>
<td>18.8</td>
<td>16.3</td>
<td>19.4</td>
<td>30.8</td>
</tr>
<tr>
<td>Moderate</td>
<td>48.9</td>
<td>51.9</td>
<td>57.3</td>
<td>58.6</td>
<td>53.4</td>
</tr>
<tr>
<td>Heavier</td>
<td>31.8</td>
<td>29.3</td>
<td>26.4</td>
<td>22.0</td>
<td>15.8</td>
</tr>
<tr>
<td>Hormone use (women) **</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>60.8</td>
<td>60.7</td>
<td>67.3</td>
<td>69.4</td>
<td>74.6</td>
</tr>
<tr>
<td>Past two years</td>
<td>23.7</td>
<td>20.5</td>
<td>21.2</td>
<td>14.4</td>
<td>4.4</td>
</tr>
<tr>
<td>Former</td>
<td>15.5</td>
<td>18.8</td>
<td>11.5</td>
<td>16.2</td>
<td>20.9</td>
</tr>
</tbody>
</table>

* Marital status, smoking status, daily alcohol consumption, and hormone use (women) assessed at exam nearest age 55 years. Nine people were missing marital status at age 55 years.
Figure 3.1: Incident coronary heart disease events (top panel; n = 1,305) and cerebrovascular accidents (bottom panel, n = 1,378) in relation to weight patterns during middle age.
Table 3.2: Rates of incident cardiovascular disease in relation to weight patterns during middle age

<table>
<thead>
<tr>
<th></th>
<th>Events / person-years</th>
<th>Rate per 1,000 person-years</th>
<th>Crude HR (95% CI)</th>
<th>Adjusted* HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHD (n = 1,305)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight, no cycling</td>
<td>88 / 7,607</td>
<td>11.6</td>
<td>(Referent)</td>
<td>(Referent)</td>
</tr>
<tr>
<td>Normal weight, cycling</td>
<td>104 / 6,234</td>
<td>16.7</td>
<td>1.5 (1.1 – 2.0)</td>
<td>1.5 (1.1 – 2.0)</td>
</tr>
<tr>
<td>Overweight, no cycling</td>
<td>86 / 3,955</td>
<td>21.7</td>
<td>2.0 (1.5 – 2.7)</td>
<td>1.5 (1.1 – 2.0)</td>
</tr>
<tr>
<td>Overweight, cycling</td>
<td>115 / 6,462</td>
<td>17.8</td>
<td>1.6 (1.2 – 2.1)</td>
<td>1.4 (1.0 – 1.8)</td>
</tr>
<tr>
<td>Obese</td>
<td>56 / 2,150</td>
<td>26.0</td>
<td>2.4 (1.7 – 3.4)</td>
<td>2.0 (1.4 – 2.9)</td>
</tr>
<tr>
<td>**CVA (n= 1,378)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight, no cycling</td>
<td>42 / 8,284</td>
<td>5.1</td>
<td>(Referent)</td>
<td>(Referent)</td>
</tr>
<tr>
<td>Normal weight, cycling</td>
<td>65 / 6,876</td>
<td>9.5</td>
<td>2.1 (1.4 – 3.1)</td>
<td>2.1 (1.4 – 3.1)</td>
</tr>
<tr>
<td>Overweight, no cycling</td>
<td>49 / 4,673</td>
<td>10.5</td>
<td>2.4 (1.6 – 3.7)</td>
<td>2.1 (1.4 – 3.3)</td>
</tr>
<tr>
<td>Overweight, cycling</td>
<td>72 / 7,236</td>
<td>10.0</td>
<td>2.3 (1.5 – 3.3)</td>
<td>2.3 (1.5 – 3.4)</td>
</tr>
<tr>
<td>Obese</td>
<td>39 / 2,598</td>
<td>15.0</td>
<td>3.7 (2.4 – 5.7)</td>
<td>4.5 (2.8 – 7.5)</td>
</tr>
<tr>
<td>**CVD (n = 1,291)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight, no cycling</td>
<td>136 / 7,453</td>
<td>18.2</td>
<td>(Referent)</td>
<td>(Referent)</td>
</tr>
<tr>
<td>Normal weight, cycling</td>
<td>150 / 5,898</td>
<td>25.4</td>
<td>1.6 (1.2 – 2.0)</td>
<td>1.5 (1.2 – 2.0)</td>
</tr>
<tr>
<td>Overweight, no cycling</td>
<td>125 / 3,811</td>
<td>32.8</td>
<td>2.1 (1.6 – 2.7)</td>
<td>1.7 (1.3 – 2.2)</td>
</tr>
<tr>
<td>Overweight, cycling</td>
<td>180 / 6,009</td>
<td>30.0</td>
<td>1.9 (1.5 – 2.4)</td>
<td>1.8 (1.4 – 2.2)</td>
</tr>
<tr>
<td>Obese</td>
<td>79 / 1,932</td>
<td>40.9</td>
<td>2.6 (2.0 – 3.5)</td>
<td>2.7 (2.0 – 3.5)</td>
</tr>
</tbody>
</table>

* CHD model adjusted for gender, smoking, education, weight status at age 25 years, and alcohol consumption; CVA model adjusted for gender, smoking, and weight status at age 25 years; CVD model adjusted for gender and smoking
Table 3.3: Mortality rates in relation to weight patterns during middle age (n = 1,387)

<table>
<thead>
<tr>
<th></th>
<th>Deaths / person-years</th>
<th>Rate per 1,000 person-years</th>
<th>Crude HR (95% CI)</th>
<th>Adjusted* HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALL-CAUSE MORTALITY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight, no cycling</td>
<td>245 / 9,457</td>
<td>25.9</td>
<td>(Referent)</td>
<td>(Referent)</td>
</tr>
<tr>
<td>Normal weight, cycling</td>
<td>213 / 8,132</td>
<td>26.2</td>
<td>1.1 (0.9 – 1.3)</td>
<td>1.0 (0.9 – 1.3)</td>
</tr>
<tr>
<td>Overweight, no cycling</td>
<td>162 / 5,424</td>
<td>29.9</td>
<td>1.3 (1.1 – 1.6)</td>
<td>1.1 (0.9 – 1.3)</td>
</tr>
<tr>
<td>Overweight, cycling</td>
<td>253 / 8,418</td>
<td>30.1</td>
<td>1.3 (1.1 – 1.5)</td>
<td>1.2 (1.0 – 1.4)</td>
</tr>
<tr>
<td>Obese</td>
<td>106 / 3,107</td>
<td>34.1</td>
<td>1.6 (1.3 – 2.0)</td>
<td>1.4 (1.1 – 1.9)</td>
</tr>
<tr>
<td><strong>CHD MORTALITY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight, no cycling</td>
<td>35 / 9,457</td>
<td>3.7</td>
<td>(Referent)</td>
<td>(Referent)</td>
</tr>
<tr>
<td>Normal weight, cycling</td>
<td>36 / 8,132</td>
<td>4.4</td>
<td>1.2 (0.8 – 1.9)</td>
<td>1.2 (0.8 – 1.9)</td>
</tr>
<tr>
<td>Overweight, no cycling</td>
<td>42 / 5,424</td>
<td>7.7</td>
<td>2.2 (1.4 – 3.4)</td>
<td>1.4 (0.9 – 2.3)</td>
</tr>
<tr>
<td>Overweight, cycling</td>
<td>49 / 8,418</td>
<td>5.8</td>
<td>1.6 (1.1 – 2.5)</td>
<td>1.3 (0.8 – 2.0)</td>
</tr>
<tr>
<td>Obese</td>
<td>22 / 3,107</td>
<td>7.1</td>
<td>2.0 (1.2 – 3.5)</td>
<td>1.5 (0.8 – 2.8)</td>
</tr>
<tr>
<td><strong>CVD MORTALITY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight, no cycling</td>
<td>60 / 9,457</td>
<td>6.3</td>
<td>(Referent)</td>
<td>(Referent)</td>
</tr>
<tr>
<td>Normal weight, cycling</td>
<td>73 / 8,132</td>
<td>9.0</td>
<td>1.5 (1.1 – 2.1)</td>
<td>1.4 (1.0 – 2.0)</td>
</tr>
<tr>
<td>Overweight, no cycling</td>
<td>57 / 5,424</td>
<td>10.5</td>
<td>1.8 (1.3 – 2.7)</td>
<td>1.4 (0.9 – 2.0)</td>
</tr>
<tr>
<td>Overweight, cycling</td>
<td>92 / 8,418</td>
<td>10.9</td>
<td>1.9 (1.4 – 2.6)</td>
<td>1.6 (1.1 – 2.2)</td>
</tr>
<tr>
<td>Obese</td>
<td>38 / 3,107</td>
<td>12.2</td>
<td>2.2 (1.5 – 3.3)</td>
<td>1.8 (1.1 – 2.9)</td>
</tr>
</tbody>
</table>

* All-cause mortality model adjusted for gender, smoking, alcohol consumption, and weight status at 25 years; CHD mortality model adjusted for gender, hormone use (women), smoking, and weight status at 25 years; CVD mortality model adjusted for gender, alcohol consumption, smoking, and weight status at age 25 years.
CHAPTER 4: INCIDENT DIABETES IN RELATION TO OVERALL WEIGHT

STATUS AND WEIGHT CYCLING DURING MIDDLE AGE
Abstract

Objective: To quantify the effect of overall weight status and weight cycling during middle age on incident diabetes.

Research Design and Methods: Participants included a subset of the Framingham Heart Study original cohort limited-access dataset (n = 1,476) who were observed from 40 to 50 years and were not diagnosed with diabetes before 50 years. A functional principal components analysis of body mass index from 40 to 50 years defined weight patterns. Using the scores from the principal component functions we jointly categorized overall weight status and weight cycling.

Results: Adults with an overall overweight trajectory who experienced cycling during middle age (adjusted hazard ratio [HR] and 95% confidence interval [CI] = 2.9; 1.8 – 4.8), those with an overall overweight trajectory who did not experience cycling (adjusted HR = 2.9; 95% CI: 1.8 – 4.6), and those with an overall obese trajectory (adjusted HR = 7.5; 95% CI: 4.7 – 12.0) had increased rates of diabetes compared to adults with an overall normal weight trajectory who did not experience weight cycling. Adults with an overall normal weight trajectory who experienced weight cycling did not have increased rates of diabetes (adjusted HR = 1.1; 95% CI: 0.6 – 1.9).

Conclusions: Overweight and obesity were associated with increased rates of diabetes but weight cycling did not add additional risk. Our findings support recommendations of weight loss among overweight and obese adults for the prevention of diabetes and suggest that cycles of weight loss and regain may not increase diabetes risk among middle-aged adults.
Introduction

Overweight and obesity increase risk of Type 2 diabetes mellitus in adults.\textsuperscript{7,10,16} Weight history provides information about diabetes risk beyond current weight\textsuperscript{4,5,7,16,38} and increased duration of obesity is associated with diabetes.\textsuperscript{4,5} Weight variability has also been linked to incident diabetes\textsuperscript{17} and high fasting glucose.\textsuperscript{39} While the influence of weight variability appears to vary across categories of baseline weight,\textsuperscript{39} the evidence is mixed whether these effects can be explained by attained weight.\textsuperscript{10,17}

In Chapter 3 of this dissertation, we found that weight cycling among normal weight individuals, but not overweight individuals, was associated with higher rates of cardiovascular disease. Given evidence that the effect of weight on cardiovascular disease is at least partially mediated through blood glucose, blood pressure, and lipids,\textsuperscript{23} we hypothesized that weight cycling would be associated with higher rates of incident diabetes among normal weight adults but not among overweight adults.

Methods

– Dataset and participants–

The Brown University IRB approved this study. We used the limited-access dataset of the Framingham Heart Study (FHS) Original Cohort.\textsuperscript{55} The design of the FHS has been described in detail elsewhere.\textsuperscript{56} Briefly, in 1948 – 1952, researchers enrolled 5,209 men and women aged 28 to 62 years without clinically apparent cardiovascular disease. Biennial study visits included an interview, clinical examination, and laboratory tests. Of the 5,079 participants who provided informed consent for inclusion in the limited-access dataset, we excluded participants who were enrolled in the FHS cohort.
after the age of 40 years (n = 3071), those who did not attend FHS exams after age 50 years (n = 218), and those missing BMI measurements for more than four consecutive years or at two or more exams during this period (n = 213), resulting in a sample of 1,577 adults for the characterization of weight patterns.

- **Characterizing weight patterns** -

  We characterized weight patterns using principal component scores derived from a functional principal components analysis of body mass index (BMI) from age 40 to 50 years. The limited-access FHS dataset included exact BMI for the majority of participant assessments. For exams for which exact BMI was not provided, we used a randomly selected weight from the 5-pound range provided to preserve participant confidentiality and proximally measured height to calculate BMI. The theory and methodology of functional principal components analysis (PCA) have been described in detail elsewhere. Briefly, this approach determines the most important ways each trajectory varies from the average trajectory and participants are scored based on how similar their weight trajectory is to each pattern.

  The first principal component (PC) function reflected differences in overall weight status. Participants with high scores on this PC function were heavier than average and participants with low scores were lighter than average, regardless of the shape of their trajectory. We categorized participants as overall normal weight (PC function 1 score in deciles 1 – 5), overweight (deciles 6 – 9), or obese (decile 10). Median (inter-quartile range) mean BMI from 40 to 50 years for these three groups were 22.8 kg/m$^2$ (21.5 to 23.9 kg/m$^2$) for overall normal weight (excluding 20 participants who were...
consistently underweight), 26.9 kg/m\(^2\) (25.9 to 28.3 kg/m\(^2\)) for overall overweight, and 32.3 kg/m\(^2\) (31.3 to 34.2 kg/m\(^2\)) for overall obese trajectories.

The third through eighth PC functions reflect weight cycling at increasing frequency. Participants with both high and low scores on these PCs exhibit cycling in their BMI curves during middle age but with gains and losses at opposite times. Scores in the highest or lowest 10% on PC functions 3 through 6 and/or in the highest or lowest 5% on PC functions 7 or 8 reflected cycling of approximately one kg/m\(^2\) or more.

We jointly categorized participants by overall weight status and weight cycling. Because only a small number of participants with an overall obese weight trajectory did not experience weight cycling, we were unable to examine the impact of weight cycling on incident diabetes among those with an overall obese trajectory. Therefore, we classified participants as overall normal weight without cycling, overall normal weight with cycling, overweight without cycling, overweight with cycling, and overall obese.

- Diabetes ascertainment -

We considered a non-fasting plasma glucose level of at least 200 mg/dL (11.1 mmol/L) and/or treatment with insulin or an oral hypoglycemic agent at a study exam as indicative of Type II diabetes mellitus. While it is possible that some participants had Type I diabetes, Type II diabetes accounts for 90 to 95% of diabetes among adults and diagnosis of Type I diabetes during middle age is unlikely.\(^{101}\)
– Potential confounders –

We considered as potential confounders variables previously found to confound the relationship between weight and diabetes. Four characteristics were not time-varying: gender, education, family history of diabetes, and weight status at 25 years. At exams 7 and 8, participants reported lifetime family history of diabetes. Participants who reported diabetes in a parent, sibling, or both at either exam were considered to have a positive family history of diabetes. To preserve confidentiality, recalled weight at age 25 years was provided in 5-pound groupings in the limited-access dataset. For the majority of participants, both the minimum and maximum possible BMI calculated from measured height at exam 1 were either in the overweight/obese (25 kg/m² ≤ BMI) or underweight/normal weight range (BMI < 25 kg/m²). For the 104 participants whose possible BMI range included 25 kg/m², we categorized their weight status at age 25 years based on a randomly selected a weight from the 5-pound range provided. We also evaluated three time-varying potential confounders. We used the most recent assessment to categorize these variables at every year of age. Current smokers included those who reported smoking cigarettes, pipes, and/or cigars since the previous FHS exam. We categorized participants as never smokers, current smokers, former smokers who quit within the past four years, and former smokers who quit more than four years ago. Alcohol was provided in the FHS limited-access dataset as ounces per week or month or number of various types of alcoholic drinks per week. We converted these data into average grams of ethanol consumed per day and categorized daily alcohol consumption as none, moderate consumption (up to 15/30 grams per day for women/men), or heavier consumption (more than 15/30 grams per day for women/men). Postmenopausal hormone
therapy has been linked to lower incidence of diabetes.\textsuperscript{102} We classified women as never or ever users of any type of hormones.

\textbf{- Statistical analyses -}

We excluded participants who were consistently underweight (n = 20), those with diabetes before age 50 years (n = 23), and those missing covariates (n = 58), resulting in a final analytic sample of 1,476 adults. We calculated the number of events and person-years of follow-up from age 50 years until first exam with indication of diabetes or last exam attended. Kaplan-Meier estimators\textsuperscript{91} provided graphical comparisons of incident diabetes across weight patterns. We estimated incidence rate ratios (IRRs) for diabetes using Cox proportional hazards models.\textsuperscript{91} We controlled for confounding by multivariable adjustment. Provided the inclusion of a potential confounder changed the estimated hazard ratio for a weight pattern category by about 10\%, the covariate that produced the greatest change in the IRR was retained in the model. Model building continued until the estimated IRR was not modified by inclusion of additional confounders. Because previous research has shown that weight cycling had no effect once weight changes are accounted for,\textsuperscript{10} we also adjusted for weight changes (PC function 2 scores: weight loss (quintile 1), neither weight loss nor weight gain (quintile 2), or weight gain (quintiles 3 – 5)). Analyses were conducted in SAS (Version 9.1.3, SAS Institute, Inc., Cary, NC) and R (www.r-project.org).
Results

Characteristics of the sample at age 50 years in relation to weight patterns are shown in Table 4.1. The gender distribution varied across the patterns: those with overall normal weight trajectories were more likely to be women and among overweight participants, those who experienced weight cycling were more likely to be women. Overall weight status was inversely associated with education. Participants with an overall obese weight pattern were more likely to abstain from alcohol use and smoking. The proportion of participants with a family history of diabetes was similar across categories of overall weight status and weight cycling.

Table 4.2 and Figure 4.1 show the relationship between overall weight status and weight cycling during middle age and incident diabetes. Overall, there were 217 cases of diabetes during 35,359 person-years of follow-up. The rate of incident diabetes among participants with a normal weight trajectory who experienced weight cycling did not differ from the rate of diabetes among normal weight non-cyclers (adjusted HR = 1.1; 95% CI: 0.6 – 1.9). While both those with an overall overweight trajectory who experienced weight cycling and those who did not experience weight cycling had increased rates of diabetes compared to normal weight non-cyclers, their increased rate ratios were very similar (adjusted HR = 2.8; 95% CI: 1.8 – 4.6 and adjusted HR = 2.9; 95% CI: 1.8 – 4.6, respectively). Participants with an overall obese trajectory had increased rates of diabetes (adjusted HR = 7.5; 95% CI: 4.7 – 12.0).

Adjustment for weight changes did not materially alter the estimated hazards ratios for overall weight status/weight cycling (data not shown) and weight changes were not associated with diabetes (adjusted HR = 1.1; 95% CI: 0.7 – 1.8 for weight loss and
adjusted HR = 1.2; 95% CI: 0.8 – 1.7 for weight gain) compared to neither weight loss nor weight gain.

Family history of diabetes did not confound the association between weight status/weight cycling and diabetes. However, independent of weight patterns and confounders, adults with a family history of diabetes had higher rates of diabetes than adults without a family history of diabetes (adjusted HR = 1.6, 95% CI: 1.2 – 2.2 for parent; adjusted HR 1.5, 95% CI: 1.1 – 2.0 for parent and/or sibling).

**Discussion**

While overall weight status during middle age was strongly associated with the development of diabetes, we did not find that weight cycling was associated with increased rates of diabetes among either adults with an overall normal weight or overall overweight trajectory. The current study adds to this body of work on the effect of weight cycling on diabetes. In their analysis of the Nurses’ Health Study II, Field et al. (2004) found that while weight cycling was associated with incident diabetes at the crude level, the higher mean BMI with increased cycling explained this finding and weight cycling had no independent effect on diabetes after adjustment for body mass index. Our analytic approach allows us to consider the effect of weight cycling at different overall weight statuses. Our findings do not support our hypothesis that among normal weight adults, weight cycling would be associated with higher rates of diabetes.

There is strong clinical trial evidence that modest weight loss can delay or prevent the development of diabetes among overweight and obese adults yet weight losses that are not maintained have not been shown to lead to reduced risk of diabetes.
Another study found that although fasting glucose and 2-hour glucose levels improved with weight loss, values returned to pre-weight loss levels with weight regain. Our finding that weight cycling did not increase diabetes incidence rates among either adults with overall normal weight or overall overweight trajectories during middle age suggests that fluctuations, while potentially resulting in short-term metabolic alterations, do not lead to increased risk of diabetes.

Our findings add to the body of evidence linking overweight and obesity during adulthood to incident diabetes. However, while many previous studies only used a few weight assessments, we show an effect of weight trajectory over eleven years during middle age on subsequent diabetes using functional methods to characterize weight histories. Functional PCA captures variation in individuals’ entire weight history over the period under study, thus allowing us to characterize weight as a time-varying and cumulative exposure. This is a strength of our study in light of evidence that the duration of overweight or obesity increases risk of diabetes. Our results did not change with adjustment for weight loss and weight gain during the period under study, indicating that the lack of an effect of weight cycling cannot be explained by an underlying trend in weight across this period. This study confirms also previous findings that a family history of diabetes is an independent risk factor for diabetes.

Height and weight were measured biannually according to standardized protocols, thus avoiding some of the known biases associated with self-reported weight. While BMI does not differentiate between lean and fat mass, BMI is highly correlated with waist circumference and is similarly related to total and abdominal fat and is recommended for the classification of overweight and obesity in adults by national
evidence-based clinical guidelines. While we were unable to detect weight cycles occurring between biennial FHS exams, more frequent cycling was likely captured as cycling of a different frequency.

We considered a non-fasting plasma glucose level of at least 200 mg/dL (11.1 mmol/L) and/or treatment with insulin or an oral hypoglycemic agent at a study exam indicative of Type II diabetes mellitus. Type II diabetes accounts for 90 to 95% of diabetes in adults and diagnosis of Type I diabetes during middle age is unlikely. Because fasting glucose measurements were not available, our definition of diabetes may be less sensitive than criteria recommended by the American Diabetes Association (ADA), and may be more likely to identify more severe cases of diabetes. Because the onset of diabetes may occur four to seven years before clinical diagnosis, the prospectively-measured plasma glucose levels in the FHS reduces the potential for an extended latency period due to clinical surveillance. Diabetes status was updated at study exams and there may be misclassification of diagnosis date. However, this misclassification is unlikely to be differential with respect to overall weight status/weight cycling and therefore may have resulted in an attenuation of the association between weight patterns during middle age and incident diabetes.

There is potential for residual confounding owing to measurement error as well as unmeasured variables. While smoking, alcohol consumption, and hormone use were assessed regularly, we could not update these variables between exams, potentially resulting in misclassification at the time of diagnosis. To assess the potential impact of error in recalled weight, we also classified weight status at 25 years after adjusting BMI by the average number of pounds recalled for groups defined by gender and weight status.
at the time of recall. We found that adjusted models using this variable resulted in very similar estimated hazards ratios for diabetes in relation to overall weight status/weight cycling (data not shown). Information about current or previous pregnancies in the FHS limited-access dataset is limited yet history of gestational diabetes and higher parity are risk factors for Type II diabetes in women. In this sample, among those with available information on physical activity, activity level was similar across weight patterns and was not associated with diabetes (N = 1,380; data not shown). Given the limited potential of physical activity to confound the association under study in this sample, the infrequency of measurement, and the relatively high proportion of participants missing physical activity, we decided not to include physical activity in our main analyses.

Because the sample was fairly lean (average BMI at 40 and 50 years were 25.2 kg/m$^2$ and 25.9 kg/m$^2$, respectively) and only 10% of the sample had an overall obese trajectory, we were unable to differentiate between levels of obesity or to examine the effect of weight cycling on diabetes incidence among individuals with overall obese trajectory. The prevalence of overweight and obesity differ by racial/ethnic groups in the United States and the relationship between weight and diabetes may differ among racial/ethnic groups. Analyses of more diverse cohorts are needed to explore the combined effects of overall weight status and weight cycling on incident diabetes.

In this study, we found that overweight and obesity over a decade during middle age were associated with increased rates of diabetes, but weight cycling was not. Our results support weight loss recommendations for overweight adults for the prevention of diabetes and cardiovascular disease. Although modest weight loss can delay or prevent the development of diabetes among overweight and obese adults, many people are
unable to maintain weight losses.\textsuperscript{51,52} However, our results suggest that regain and subsequent weight loss attempts may not increase diabetes risk among overweight patients.
Tables and Figures

Figure 4.1: Incident diabetes in relation to overall weight status and weight cycling from 40 to 50 years (N = 1,476)
Table 4.1: Characteristics of the sample at age 50 years in relation to overall weight status and weight cycling during middle age (n = 1,476), %

<table>
<thead>
<tr>
<th></th>
<th>Normal weight No cycling</th>
<th>Normal weight Cycling</th>
<th>Overweight No cycling</th>
<th>Overweight Cycling</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>410</td>
<td>312</td>
<td>248</td>
<td>353</td>
<td>153</td>
</tr>
<tr>
<td>Female</td>
<td>67.8</td>
<td>70.8</td>
<td>27.0</td>
<td>47.9</td>
<td>47.7</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>23.4</td>
<td>28.2</td>
<td>35.5</td>
<td>31.4</td>
<td>33.3</td>
</tr>
<tr>
<td>Completed high school</td>
<td>40.2</td>
<td>39.1</td>
<td>33.9</td>
<td>40.8</td>
<td>47.1</td>
</tr>
<tr>
<td>More than high school</td>
<td>36.3</td>
<td>32.7</td>
<td>30.7</td>
<td>27.8</td>
<td>19.6</td>
</tr>
<tr>
<td>Overweight or obese at 25 years</td>
<td>6.1</td>
<td>4.8</td>
<td>27.8</td>
<td>32.0</td>
<td>69.9</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent</td>
<td>13.9</td>
<td>13.1</td>
<td>16.5</td>
<td>16.2</td>
<td>17.0</td>
</tr>
<tr>
<td>Parent / sibling</td>
<td>18.1</td>
<td>17.3</td>
<td>19.8</td>
<td>20.4</td>
<td>20.3</td>
</tr>
<tr>
<td>Smoking status *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>27.6</td>
<td>20.8</td>
<td>24.6</td>
<td>27.2</td>
<td>34.6</td>
</tr>
<tr>
<td>Current</td>
<td>57.1</td>
<td>64.1</td>
<td>58.1</td>
<td>54.4</td>
<td>51.0</td>
</tr>
<tr>
<td>Quit &lt;= 4 years ago</td>
<td>5.6</td>
<td>6.7</td>
<td>5.2</td>
<td>7.9</td>
<td>2.0</td>
</tr>
<tr>
<td>Quit &gt; 4 years ago</td>
<td>9.8</td>
<td>8.3</td>
<td>12.1</td>
<td>10.5</td>
<td>12.4</td>
</tr>
<tr>
<td>Daily alcohol consumption *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>20.2</td>
<td>15.4</td>
<td>13.7</td>
<td>21.5</td>
<td>30.7</td>
</tr>
<tr>
<td>Moderate</td>
<td>55.1</td>
<td>53.2</td>
<td>62.5</td>
<td>53.5</td>
<td>52.9</td>
</tr>
<tr>
<td>Heavier</td>
<td>24.6</td>
<td>31.4</td>
<td>23.8</td>
<td>24.9</td>
<td>16.3</td>
</tr>
<tr>
<td>Ever use of hormones (women) *</td>
<td>20.9</td>
<td>26.2</td>
<td>19.4</td>
<td>17.2</td>
<td>19.2</td>
</tr>
</tbody>
</table>

* Based on latest assessment before/at age 50 years
Table 4.2: Diabetes rates in relation to overall weight status and weight cycling during middle age (N = 1,476)

<table>
<thead>
<tr>
<th>Weight Status</th>
<th>Cases / person-years</th>
<th>Rate per 1,000 person-years</th>
<th>Crude HR (95% CI)</th>
<th>Adjusted* HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal weight, no cycling</td>
<td>26 / 10,796</td>
<td>2.4</td>
<td>(Referent)</td>
<td>(Referent)</td>
</tr>
<tr>
<td>Normal weight, cycling</td>
<td>20 / 7,657</td>
<td>2.6</td>
<td>1.1 (0.6 – 2.0)</td>
<td>1.1 (0.6 – 1.9)</td>
</tr>
<tr>
<td>Overweight, no cycling</td>
<td>44 / 5,602</td>
<td>7.9</td>
<td>3.4 (2.1 – 5.6)</td>
<td>2.9 (1.8 – 4.8)</td>
</tr>
<tr>
<td>Overweight, cycling</td>
<td>64 / 8,190</td>
<td>7.8</td>
<td>3.4 (2.1 – 5.3)</td>
<td>2.9 (1.8 – 4.6)</td>
</tr>
<tr>
<td>Obese</td>
<td>63 / 3,112</td>
<td>20.2</td>
<td>9.2 (5.8 – 14.5)</td>
<td>7.5 (4.7 – 12.0)</td>
</tr>
</tbody>
</table>

* Adjusted for smoking, alcohol consumption, weight status at 25 years, education, gender, and ever hormone use (women).
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