Long-Term Body Weight Trajectories and Mortality in Older Adults: Hierarchical Clustering of Sparse Functional Data.

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ABSTRACT

To resolve the obesity paradox, researchers have increasingly focused on analyzing long-term weight changes and their effect on mortality. Analysts used fully parametric (regression) or semi-parametric (latent class) models, which required difficult-to-justify decisions that sometimes yielded conflicting findings. We propose a cutting-edge nonparametric approach -- functional data analysis for sparse longitudinal data, specifically hierarchical clustering of functions estimated via the PACE algorithm -- to estimate classes of BMI functions and identify mortality risks in each. Data are from the Health and Retirement Study (N=9,893). We found three BMI trajectory clusters for each gender: normal stable, overweight gaining, and overweight losing. The mortality of the first two groups was similar while individuals in the overweight losing cluster experienced significantly higher risk of dying. The study highlights the potential of functional data analysis for BMI trajectories, as well as many other developmental and age-dependent processes relevant to population health.
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The relationship of body mass index (BMI) and mortality among older adults has been studied extensively but critical questions remain open (1-3). Body mass index changes continuously across age, with individuals gaining or losing weight over time. However, the vast majority of previous studies on the topic have used BMI information measured at a single time point (4-9). These studies showed overweight and sometimes even obese older adults tended to have lower mortality risks compared to their peers in the normal BMI range. Many researchers, however, suspected that this pattern is a result of confounding by preexisting illness so that low BMI in a large proportion of older samples is caused by weight loss due to illness, which also causes early death (10-12).

The recognition of importance of BMI changes over time for mortality grew just as more panel surveys offered repeated information on body weight. Researches began studying these changes – albeit typically using just two time points to calculate a BMI change over time (13-19). In recent years, there has been a growing interest in methods that would reflect and incorporate the available wealth of longitudinal information rather than discard most of it. In addition, more researchers have been interested in person-centered longitudinal analyses where the data themselves reveal the typical BMI trajectories among older adults, as well as the associated health or mortality levels. It is known that distinct BMI trajectory types exist among older adults (3, 20). So far, however, we are aware of only one previous study that tried to estimate and cluster BMI trajectories and evaluate their associated survival (20). That study used a joint growth mixture-survival analysis, where a drawback was that the authors had to specify a parametric –linear-- function of time (age), which may be an inadequate representation of the actual changes in BMI as people age.

The present study uses hierarchical clustering of (sparse) functional data, a powerful, cutting-edge, nonparametric approach to analyzing longitudinal data. The methodology has only recently been developed in the statistical literature and, to the best of our knowledge, the
present study is the first use for examining substantive (applied) questions. In functional data analysis, the observed BMI data points on an individual are assumed to be representative of underlying BMI curves. We use hierarchical clustering of the curves, which allows the data to reveal the typical BMI curves in the sample. We can then examine the health and mortality differences across these clusters. The findings thus provide a clear, purely data-driven picture of the most typical patterns of body weight trajectories in older adults, and may thus help inform public-health and clinical recommendations.

MATERIALS AND METHODS

Data

We used data from the Health and Retirement Survey (21). The HRS is a nationally representative panel survey of U.S. adults born between 1931 and 1941. It is considered among leading sources of information on health of older Americans. The sample cohort was first interviewed in 1992 and re-interviewed every two years thereafter. We use data through the 2010 interview, the most recent wave available, which provides up to ten measures of BMI and mortality follow-up over 18 years of the study period. We used version L of the dataset available from the RAND Corporation (22).

Sample definition. After excluding 3 individuals who had no BMI information at any wave and 286 individuals (2.8 percent) who had BMI values considered to be outliers (above 45 or below 15 at any interview wave), the final sample size was N=9,893.

Variables

Body mass index (BMI) was calculated as weight in kg/height in m squared. Height was self-reported at the first interview; weight was self-reported at every interview. For each individual, all available BMI data points were included to define the weight functions.

Mortality followup has been collected throughout the study duration by the HRS staff who obtain information about a respondent’s death from a spouse, another family member, friend, or other sources. Individuals were coded as 0 if they survived or were believed to be alive through wave
10 in 2010; 1 if they were known or believed to have died. There were no missing values on this variable.

Covariates included age, sex, and initial health status. Age was calculated as a time-varying measure, using the year of birth and the year of each interview; it is used as the time axis for the BMI curves. Sex was dichotomized; all analyses were estimated independently for men and women. Initial health status was captured with two self-reported indicators. Self-rated health (SRH) was measured on the standard 5-point scale from excellent (=1) to poor (=5). The number of chronic conditions was a count variable ranging from 0 up to 8 (although no respondent reported having all eight conditions, which included highly prevalent conditions like hypertension, arthritis, cancer, diabetes). Both health variables were included in analyses as continuous.

Approach

We used a novel approach to identify groups of similar BMI curves: hierarchical clustering of sparse functional data. Here we describe the approach in a broad conceptual way; we include references for readers interested in additional information about the methodology.

Functional data analysis (FDA). FDA is a relatively new, flexible, nonparametric approach to modeling panel data. Within FDA, methods for densely sampled and sparsely sampled data need to be distinguished. Functional data analysis for dense data (with continuous or frequent measurements over time, as may be available with weather or climate information or from fMRI, for instance) has been well developed during the previous decade or two; excellent resources are available (23-24). In contrast, social research longitudinal data, including the repeated BMI measurements in the Health and Retirement Study, is sparse and measured with error. These characteristics necessitate a different set of methods within FDA; these methods have only recently began receiving attention (25). In fact, most of the statistical theory and computing algorithms have been developed in the past few years. To the best of our knowledge, this is the first public-health study (or indeed any substantive paper outside statistics) using FDA for sparse longitudinal data.
**FDA for (sparse) longitudinal data.** We assume that a smooth (twice-differentiable) process generates the body mass index trajectories across age (26). The BMI curves for individuals are considered i.i.d. realizations of that process. The observed data points (BMI reports at each interview) are snapshots of those individual curves at the times of measurement. The goal of FDA is to model the observed BMI data as curves with the aim of making inferences about the BMI trajectories. The unit of analysis is the BMI curve, which combines all available BMI measurements per person. As noted above, observations from longitudinal studies tend to be sparse and irregular with respect to the time variable (age in our study); sparse and irregularly spaced data are more difficult to analyze than their dense and regularly spaced counterparts. Thus, FDA methods for sparse and irregular data have complex theoretical origins (27-28), although many procedures can now be implemented with some specialized code available in the Matlab and R packages.

**First steps in FDA.** The mean function (mean BMI function by age in our case) is estimated with a local linear scatterplot smoother fitted to the aggregated BMI data plotted against age. Using the sample mean function and each individual's BMI trajectory, residuals are calculated and outliers are removed, since in later steps we need robust estimates of mean and covariance functions. Next, the mean function is combined with the raw data to calculate raw covariances of pairwise time points of BMI measurements for each individual. A final smooth covariance surface is estimated by fitting a 2-dimensional smoother over the combination of the raw covariances for all individuals. Note that for this smoothing, the diagonal covariances are underestimates of the variances and are removed, because the diagonal elements combined with the variance of measurement errors provide the final variances. Using the estimated mean function and covariance surface, principal component scores can be obtained for each individual for use in further analysis.

**Functional principal component analysis** (FPCA) is the core dimension-reduction tool in FDA (29). Analogous to multivariate principal components analysis, FPCA decomposes the covariance surface into eigenvalues and eigenfunctions (30). A small number of first eigenfunctions are chosen such that a high percentage of the variation, as given by the
eigenvalues, is explained. The FPC scores for each individual then can be obtained using the mean function and the eigenfunctions.

**FPCA via PACE.** The FPCA for sparse longitudinal data involves an additional conditional expectation and uses the Principal Analysis by Conditional Expectation (PACE) algorithm. The Principal Analysis by Conditional Expectation (PACE) approach to FPCA was recently developed by Yao, Müller, and Wang as a non-parametric approach to predicting the individual FPC scores from sparse longitudinal data; the details of the approach are available elsewhere (28). Due to the small number of observations per individual function, the FPC scores cannot be estimated effectively using the data alone but require an additional model step that combines the available individual data points with data from the whole sample (28). In the PACE approach, we assume that the FPC scores and the errors are jointly normal and thus, instead of the scores, the conditional expectation of the scores is estimated based on the estimated mean and eigenfunctions (31). The predicted FPC scores can be used to predict complete individual functions or can be used in other analyses.

**Clustering for sparse functional data.** In general, cluster analysis is an exploratory approach for grouping subjects into meaningful clusters based on their observed data. The basic idea is that the units within clusters are more similar to one another than units from other clusters. In general, the clustering procedure comprises two steps; first, a dissimilarity matrix is calculated, then clustering algorithms are used to group various features of the functional data. For the present calculation, we use the traditional cluster definition in which each subject can belong to one and only one cluster. A definition of (dis)similarity is therefore needed: $L^2$ distance is used for capturing the distance between functions (analogous to Euclidian distance for multivariate data). We follow Peng and Müller’s (32) approach for calculating the conditional pairwise $L^2$ distance between all the individuals in the sample. The resulting matrix, referred to as a dissimilarity matrix, consists of distances between BMI trajectories. Note that this conditional $L^2$ distance can be written in terms of the eigenfunction expansions of the covariance surface, thus linking it back to the tools used in FPCA.
To aid visualization and interpretation, multidimensional scaling is applied to the dissimilarity matrix to project all individual trajectories onto a 2-dimensional space. These locations are then entered into a hierarchical clustering algorithm. For this analysis, we used Ward’s linkage (33) and a squared Euclidean metric to obtain a solution with the optimal number of clusters.

Hierarchical clustering. Matlab hierarchical clustering supports an agglomerative method (bottom-up) in which smaller clusters are joined to create larger clusters as the algorithm proceeds. In the first step, each point is its own cluster. Then, the dissimilarity of all pairwise available clusters are calculated and the two clusters with the least dissimilarity are connected to create a new cluster. Now, the remaining clusters and the new cluster which contains all the individuals of the two connected clusters are used to update the dissimilarity information. The algorithm keeps repeating until only one cluster remains. The linkage and the metric determine the dissimilarity and the distance measurements, respectively. The process is usually visualized by a dendrogram, a branching diagram where clusters at one level are grouped into larger clusters at a higher level, to represent the dissimilarity across clusters or arrangement of clusters produced by hierarchical clustering. The bottom row represents collapsed data (if we had fewer than 30 observations, the original data would be shown); the other nodes represent the corresponding clusters. The length of the vertical lines represents the dissimilarity (distance) of the cluster from other clusters. The horizontal distance is irrelevant. For a clustering analysis of dense functional data, see Huzurbazar and Humphrey (34).

Documentation for the hierarchical clustering in Matlab is available online (35).

All analyses were stratified by gender. Stata 11.2 (36) was used for descriptives and for comparing the characteristics of the clusters; PACE 2.16 package in Matlab (37) was used for functional data analysis. All P-values are two-sided.

RESULTS

Table 1 summarizes characteristics of the HRS sample. The FPCA via PACE approach first estimated the mean BMI trajectories, the covariance surface, eigenfunctions, and the individuals’ estimated principal component scores. To illustrate, Figure 1 shows the estimated
mean BMI curve for men and women, the estimated correlation surface, and a scree plot from
the FPCA. The scree plot displays the cumulative proportion of total variance in the data due to
each added functional principal component. For both genders, the first two principal
components explain approximately 97 percent of the total variance in BMI. Therefore, we use
the two PC scores to represent each BMI curve for hierarchical clustering.

The dendrograms for male and female BMI data in Figure 2 show the formation of the clusters
by displaying the vertical distances between the hierarchically-formed clusters. By observing
the dendrograms, we can identify the number of clusters associated with a particularly large
vertical distance values of the cluster formation. The visual inspection indicated the 3-cluster
solution as the optimal choice for both genders. Once individuals are clustered, we can obtain
the mean BMI curves for each cluster.

Figure 3 shows the mean BMI curves in each cluster for men and women. The results for both
genders are substantively similar. One group is on average in the normal BMI range (high-
normal for men) with a relatively stable levels: a slight increase of less than 2 BMI points from
age 50 until about age 75 when the mean declines somewhat; we call this group the normal-
stable cluster. The mean BMI of the second group starts in the overweight range and increases
to the obese range; we call this group the overweight-gaining cluster. For women, this cluster
starts with the mean BMI of about 29 and increases to about 31 by age 70, at which point the
gains stop; the men’s cluster starts with the mean BMI of about 27 and increases to almost 32.
The third group is characterized by BMI curves that start in the overweight/obese range and
decline fairly steeply with age; we refer to this group as the overweight-losing cluster. For men,
the decline is about 5 BMI points from about 31 to 27; the women’s cluster declines about 7 BMI
points from 28 to 21.

Table 2 compares basic characteristics of these three groups for men and women – we
compared the two overweight clusters against the normal-stable group using simple regression-
based Wald tests. Unsurprisingly, the mean BMI levels at the start (1992) and end of followup
(2010), as well as BMI change over time, were significantly different in both overweight, non-
stable groups, compared to the reference cluster. Baseline health as measured by self-rated health and number of conditions was significantly worse for both overweight groups in both genders ($P < .001$ in seven out of the 8 comparisons, the exception was SRH in the overweight-gaining group for men, where $P = .07$). The differences were quite pronounced: for instance, the normal stable groups averaged 0.8 chronic conditions in both genders in 1992 while the overweight-losing cluster started with 1.3 and 1.4 conditions for men and women, respectively. Finally, we found interesting patterns in survival through the last 2010 wave across the groups. The overweight gaining cluster, compared to the normal stable cluster, was either statistically equivalent (for women, $P = .66$) or even experienced a lower proportion of loss to death (for men, the overweight gaining cluster lost 24 percent of the baseline individuals to mortality compared to 28 percent in the normal stable group, $P = .02$). In contrast, the overweight losing group experienced a significantly higher proportion of loss to death. Among men, 37 percent of the overweight losing cluster died through 2010, compared to 28 percent in the normal stable cluster ($P < .001$). The difference was particularly large for women: the overweight losing cluster lost over 36 percent of the sample to death, compared to just 17 percent in the normal stable group ($P < .001$).

DISCUSSION

The aim of this study was to present a novel, powerful approach to analyzing age-related changes in BMI: functional data analysis (FDA) for sparse longitudinal data. In this application, we aimed to identify typical BMI trajectories using hierarchical clustering of functional data and to determine the mortality associated with different trajectory types. To the best of our knowledge, this is the first applied paper using FDA methods for sparse data in any field.

Substantively, the approach yielded interesting findings. The BMI curves among older adults fall into three typical groups: one cluster is mostly in the normal-weight range and remains fairly stable across age; another cluster is mostly in the overweight range and characterized by gradual weight gain; a third cluster is also mostly in the overweight range but is characterized by steady weight loss. Interestingly, both the optimal number of clusters and the mean BMI curves
in each cluster were similar for men and women, which suggests common underlying biological
determinants for these three different BMI patterns. The three clusters differ substantially in
terms of initial health and survival over time. The overweight gaining cluster started with
significantly worse health than the normative normal stable cluster but experienced similar or
even slightly lower risks of dying over time. This discrepancy between health and mortality
results might be related to the obesity paradox (19) whereby overweight (and sometimes even
obese older individuals) have comparable or lower mortality than the normative group with BMIs
between 18.5 and 25.

The group that stood out in terms of both health and mortality was the overweight losing cluster.
The individuals in this group started, on average, with significantly worse health than those in
the normal stable group and they also experienced significantly greater mortality: about a third
higher among men and over twice as high among women. This comparison corroborates the
well-known high mortality following weight loss among older adults (15-16, 38). However, our
approach was able to show that the typical weight loss patterns occurs at relatively high BMI
levels, from overweight/obese levels toward the normal weights. This is an important detail
because weight loss from overweight levels could be viewed as a positive changed from the
perspective of clinicians or the individuals themselves.

We are aware of only one previous study that estimated and clustered BMI trajectories among
older adults and determined mortality differences among the groups (20). That study used a
joint growth mixture-survival (proportional hazard) model. Despite the very different
methodologies used, with fundamentally different assumptions (in particular, the FDA approach
makes no parametric assumptions about the age effects while the growth mixture analysis was
parametric—linear—with respect to time), the findings of these two studies were substantively
similar, which strengthens the validity of both sets of findings.

Several caveats should be noted. First, we did not distinguish between voluntary and
involuntary weight loss (we didn’t have the information). However, given the modest (at best)
success rates of voluntary weight loss programs in the U.S. (39-40), we can safely assume the
bulk of the weight loss observed in our data was involuntary. Second, all BMI information was self-reported, potentially inducing bias to the results. However, we do not believe the bias is problematic: most respondents tend to underreport their body weight, but presumably this underreporting is relatively unchanged over the multiple interviews. Thus the overall shape of the described trajectories is likely unbiased, but they may in reality be placed at slightly higher BMI levels.

We introduced functional data analysis as a compelling tool to analyze changes in individual characteristics across age. The approach can be used for a wide variety of substantive issues, from physical and mental development in early life to health changes across the entire lifecourse. The nonparametric nature of the FDA allows detecting subtle but possibly important features of the data, such as acceleration or deceleration of changes at specific ages or time points. For instance, in analyses not shown, we found a systematic acceleration of weight loss starting at least several years prior to death, a pattern that’s difficult to capture in parametric models. The FDA for longitudinal data is in its early years but new tools are being developed. We used hierarchical clustering but FDA can also be used for functional regression, an application likely of interest to many substantive areas. We urge researchers to explore FDA to examine diverse substantive questions because its flexibility and assumptions that differ from most standard approaches can reveal new and important findings.
REFERENCES


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36. StataCorp. Stata Statistical Software: Release 11.0. College Station, TX: StataCorp LP. College Station, TX, 2009.
Table 1. Characteristics of the HRS cohort 1992-2010, by sex (N=9,893).

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of sample at baseline</td>
<td>48.2%</td>
<td>51.8%</td>
</tr>
<tr>
<td>Mean year of birth (s.d.)</td>
<td>1936.1 (3.1)</td>
<td>1936.2 (3.1)</td>
</tr>
<tr>
<td>Mean body mass index (BMI), in kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In 1992</td>
<td>27.1 (4.0)</td>
<td>26.6 (4.9)</td>
</tr>
<tr>
<td>In 2010</td>
<td>28.0 (4.6)</td>
<td>27.5 (5.3)</td>
</tr>
<tr>
<td>Self-rated health at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>23.1%</td>
<td>21.3%</td>
</tr>
<tr>
<td>Very good</td>
<td>27.7%</td>
<td>28.6%</td>
</tr>
<tr>
<td>Good</td>
<td>28.4%</td>
<td>27.1%</td>
</tr>
<tr>
<td>Fair</td>
<td>12.8%</td>
<td>15.4%</td>
</tr>
<tr>
<td>Poor</td>
<td>8.0%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Number of conditions at baseline (s.d.)</td>
<td>1.0 (1.1)</td>
<td>1.1 (1.1)</td>
</tr>
<tr>
<td>Mortality followup</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion died by 2010 (wave 10)</td>
<td>29.2%</td>
<td>20.5%</td>
</tr>
<tr>
<td>Proportion died between waves 9 &amp; 10</td>
<td>7.2%</td>
<td>5.8%</td>
</tr>
<tr>
<td>N</td>
<td>4,764</td>
<td>5,129</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------------------------------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>% in each class</td>
<td>39.1%</td>
<td>33.9%</td>
</tr>
<tr>
<td></td>
<td>32.1%</td>
<td>50.9%</td>
</tr>
<tr>
<td></td>
<td>28.8%</td>
<td>15.1%</td>
</tr>
<tr>
<td>BMI at 1992 baseline</td>
<td>24.1 Ref.</td>
<td>22.2 Ref.</td>
</tr>
<tr>
<td></td>
<td>27.4 ( P &lt; .001 )</td>
<td>29.3 ( P &lt; .001 )</td>
</tr>
<tr>
<td></td>
<td>30.7 ( P &lt; .001 )</td>
<td>27.5 ( P &lt; .001 )</td>
</tr>
<tr>
<td>BMI at 2010 interview</td>
<td>24.6 Ref.</td>
<td>23.5 Ref.</td>
</tr>
<tr>
<td></td>
<td>31.5 ( P &lt; .001 )</td>
<td>31.0 ( P &lt; .001 )</td>
</tr>
<tr>
<td></td>
<td>29.1 ( P &lt; .001 )</td>
<td>22.7 ( P &lt; .001 )</td>
</tr>
<tr>
<td>BMI change 1992 to 2010</td>
<td>0.2 Ref.</td>
<td>1.1 Ref.</td>
</tr>
<tr>
<td></td>
<td>3.4 ( P &lt; .001 )</td>
<td>2.1 ( P &lt; .001 )</td>
</tr>
<tr>
<td></td>
<td>-1.5 ( P &lt; .001 )</td>
<td>-4.6 ( P = .001 )</td>
</tr>
<tr>
<td>Year of birth</td>
<td>1935.8 Ref.</td>
<td>1936.1 Ref.</td>
</tr>
<tr>
<td></td>
<td>1936.5 ( P &lt; .001 )</td>
<td>1936.3 ( P &lt; .001 )</td>
</tr>
<tr>
<td></td>
<td>1936.3 ( P &lt; .001 )</td>
<td>1936.3 ( P = .223 )</td>
</tr>
<tr>
<td>Self-rated health</td>
<td>2.4 Ref.</td>
<td>2.3 Ref.</td>
</tr>
<tr>
<td></td>
<td>2.5 ( P = .075 )</td>
<td>2.7 ( P &lt; .001 )</td>
</tr>
<tr>
<td></td>
<td>2.8 ( P &lt; .001 )</td>
<td>2.9 ( P &lt; .001 )</td>
</tr>
<tr>
<td>Number of conditions</td>
<td>0.8 Ref.</td>
<td>0.8 Ref.</td>
</tr>
<tr>
<td></td>
<td>1.0 ( P &lt; .001 )</td>
<td>1.2 ( P &lt; .001 )</td>
</tr>
<tr>
<td></td>
<td>1.25 ( P &lt; .001 )</td>
<td>1.4 ( P &lt; .001 )</td>
</tr>
<tr>
<td>Proportion died by 2010</td>
<td>27.7% Ref.</td>
<td>17.4% Ref.</td>
</tr>
<tr>
<td></td>
<td>24.2% ( P = .023 )</td>
<td>17.9% ( P = .664 )</td>
</tr>
<tr>
<td></td>
<td>36.6% ( P &lt; .001 )</td>
<td>36.1% ( P &lt; .001 )</td>
</tr>
</tbody>
</table>

Note: The first column for each group summarizes each characteristic within the group. The second column shows the p-value comparing the second and third groups with the first one with respect to each characteristic. The results are from regression models (linear models, ordered logistic models for SRH and logistic models for proportion who died) of a characteristic on the categorical cluster variable, with the “stable normal” group as the reference category. The summarized mean BMI levels in each cluster listed in this table are not identical to the estimated mean cluster BMI trajectories.
Figure 1. Mean BMI curves, fitted correlation surfaces, and scree plots.

Note: the left and right panel show results for men and women, respectively.
Figure 2. Dendrograms for male and female clustering, respectively.
Figure 3. The mean BMI curves of each clusters for men and women

Note: NS = normal stable cluster; OG = overweight gaining cluster; OL = overweight-losing cluster.