Chapter 5
Predicting Mortality from Profiles of Biological Risk and Performance Measures of Functioning

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Abstract While high-risk levels of individual biological and functioning indicators are predictive of adverse health outcomes, the use of measures that incorporate multiple measures is often a better indicator of current health and a better predictor of health outcomes than any single marker. Using the latent class approach and multiple markers indicating functioning across several physiological systems, this study groups individuals into risk classes for mortality. Participants age 60+ from the US National Health and Nutrition Examination Survey III (1988–1994) were included ($N = 3{,}120$), and logistic regression models were used to determine the relationship between the latent risk classes and 5-year mortality. The indicators examined included a number of biomarkers and measures of physiological and mental conditions. With the ten physiological indicators and five functioning/frailty indicators, individuals were categorized into four latent classes termed: no high-risk, high inflammation, high blood pressure, and high frailty. Compared to the no high-risk class, participants in the high inflammation and high frailty classes were 2.6 and 2.8 times as likely to die within 5-years of the initial exam (respectively); people in the high blood pressure class were 1.8 times as likely to die relative to the no high-risk class. Based on the ability of the latent class approach to predict 5-year mortality, we suggest that this approach to classifying individuals based on their biological and functioning indicators is an appropriate method for grouping people into classes indicating their risk of death.

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J. Anson, M. Luy (eds.), *Mortality in an International Perspective,*
European Studies of Population 18, DOI 10.1007/978-3-319-03029-6_5,

Keywords Biomarkers · Latent classes · Performance indicators · Risk factors · United States

5.1 Introduction

A number of biomarkers, either individually or as part of summary indices, have been predictive of morbidity, disability, and mortality in older adult populations (Crimmins et al. 2003; Goldman et al. 2006; Karlamangla et al. 2002, 2006; McEwen and Stellar 1993; Wang et al. 2007). Researchers have more recently focused on how combinations of biomarkers improve prediction of these health outcomes. A variety of methods using multiple biomarkers have been used, but additional methods that increase our understanding of how constellations of factors operate deserve consideration. This study examines the utility of the latent class approach to predicting mortality using a wide-ranging set of physiological, cognitive, and physical functioning indicators by grouping individuals into latent risk classes. Our analysis builds on earlier work that has used multiple indicators (e.g., allostatic load and metabolic syndrome) to determine the risk for a given health outcome.

5.2 Approaches to Summary Measures

One of the earliest attempts to categorize multiple biological indicators for predicting risk of mortality and cardiovascular events is the widely used Framingham risk score (Wilson et al. 1998). The MacArthur Study of Successful Aging was also used to create a summary measure based on a wider range of physiological systems. The summary score initially included 10 biological markers representing activity in the metabolic, cardiovascular, hypothalamic-pituitary axis (HPA), and sympathetic nervous system (SNS) (Seeman et al. 1997). While a number of studies have found this method to be predictive of several outcomes prevalent in aging populations (Gruenewald et al. 2009; Karlamangla et al. 2006; Seeman et al. 2001), this operationalization is limited in three respects: (1) its simple method of summing the total number of elevated-risk biomarkers, (2) its equal weighting of all biomarkers, and (3) the health domains included. In using cutpoints based on elevated-risk levels, the approach does not allow for full consideration of risk associated with the range of values for a given biomarker. In equally weighting risk factors, the approach does not incorporate the fact that some biomarkers may differentially predict health outcomes (Crimmins and Vasunilashorn 2011; Turra et al. 2005).

As an alternative to summing scores and using equal weight, canonical correlation analysis, which utilizes weights for the summation of standardized biomarker scores, has been used (Karlamangla et al. 2002). The goal of this method is to determine which linear combination of biomarkers is most related to a given linear combination of changes in outcome scores. Karlamangla et al. (2002) found markedly larger correlations between this biomarker summary method and subsequent functional

decline than reported in previous studies of summary measures using an equally weighted count of the total number of at-risk indicators of dysregulated systems. Using a similar computational method to examine change in summary measures over-time, Karlamangla et al. (2006) also found that individuals with an increased biomarker risk score had higher risk of all-cause mortality over a 7-year period compared to those who exhibited a decrease in allostatic load score.

Recursive partitioning (RP) of individuals into low, intermediate, and high allostatic load categories is another approach to creating a biomarker summary score. To perform this technique, a set of predictor biomarker variables is identified and a well-established outcome, such as mortality, is defined. Once these are established, the recursive partitioning algorithm searches among the predictor biomarker variables and their cutpoints to determine the best single predictor variable and its corresponding cutpoint. Individuals are then partitioned into two groups, with individuals on one side of the cutpoint predicted to be in one of the outcome categories while individuals on the other side of the cutpoint are predicted to reside in the alternate outcome category (Zhang and Singer 1999). Using the MacArthur Study of Successful Aging, Gruenewald et al. (2006) illustrated the utility of RP techniques to identify biomarker classifications predictive of 12-year mortality.

A fourth approach uses factor analysis to investigate the relationships among individual biomarkers by grouping markers into system-specific factors. For instance, Kubzansky et al. (1999) observed three general factors to which they termed metabolic dysregulation, cardiovascular function, and SNS activity, which they associated with low educational attainment and hostility. Using some similar and additional biomarkers, Nakamura and Miyao (2003) also detected three system-specific factors related to pulmonary function, hematology, and protein metabolism. Among insulin resistant individuals, Sakkinen et al. (2000) examined 21 biomarkers that were grouped into seven factors associated with insulin resistance syndrome: body mass, inflammation, Vitamin K dependent proteins, insulin/glucose, procoagulation, blood pressure, and lipids.

We propose to use latent class analysis, a potentially promising approach for considering multiple indicators collected at one timepoint. This is an appropriate method of classifying individuals based on multiple biological and functioning indicators that represent functioning across several physiological systems by identifying clusters of individuals who share similar biological and functioning profiles. The latent class approach also allows for consideration of a multi-physiological system without depending on a given outcome for categorization. This is in contrast to the recursive partitioning method that requires an outcome measure (e.g., mortality) to categorize individuals with a given biological profile (as used by Gruenewald et al. (2006)). In other words, the latent class approach instead groups people based solely on the independent variables (biomarker or functioning indicators) and does not require an outcome variable in its classification process. The latent class approach has been used to classify individuals on a variety of health risk measures, including childhood disadvantage (Hamil-Luker and O'Rand 2007; O'Rand and Hamil-Luker 2005) and health risk behaviors (Laska et al. 2009). No studies, to our knowledge, have used this approach to classify individuals based on their biological profiles.

As indicated above, health domains included in summary measures have generally included indicators of cardiovascular health, metabolic indicators, inflammatory markers and indicators of functioning of SNS and HPA. In addition to indicators of physiological state, markers of functioning have also been predictive of future adverse outcomes (Crimmins et al. 2010; Guralnik et al. 1989; Newman et al. 2006). Along with the biomarkers generally included in summary measures, indicators of cognitive, kidney, lung, and physical function were found to be predictive of 5-year mortality, particularly among older persons (Crimmins et al. 2010).

The purpose of this study is to investigate how biomarkers and performance measures of functioning can be used to classify individuals into risk profiles using the latent class approach. The latent classes determined by this approach will be used to determine the utility of this categorization to predict subsequent mortality. It is hypothesized that this approach to classifying individuals based on their at-risk biomarker and functioning indicator profiles will yield additional useful information about how to categorize and better understand the meaning of risk profiles. This would provide another analytic technique for operationalizing health using an individual's biological risk and frailty profile as a means of classification.

5.3 Materials & Methods

5.3.1 Study Population

Participants with linked mortality data from the National Health and Nutrition Examination Survey (NHANES) III [1988–1994] aged 60 and older were included in the study. The NHANES is designed to regularly monitor the health and nutritional status of the American noninstitutionalized population. Every year approximately 5,000 people undergo detailed interviews and medical examinations that include several physiological measures and laboratory tests. US counties are the primary sampling units for this survey, which uses a complex sampling design requiring that weights be applied in analysis to make the sample representative of the US population.

Individuals with follow-up mortality data for the 5-years after their examination in the NHANES survey were included in our analysis ($N = 3{,}120$). Mortality and cause-of-death information were accessed from data linked to the National Death Index (NDI). The NDI has been shown to have very high sensitivity and specificity and is regarded as the best source of mortality data for survey matching (Cowper et al. 2002). Since we are interested in the classification of biomarkers related to mortality among non-violent, non-accidental deaths, we excluded individuals with violent or accidental causes of death based on the International Classification of Diseases, Injuries, and Causes of Death (ICD-10) ($N = 16$). This includes individuals dying from motor accidents ($N = 5$), falls ($N = 5$), other non-transport accidents ($N = 1$), suicide ($N = 2$), homicide ($N = 3$), or medical/surgical care complications ($N = 1$). Given the small number of individuals who died of certain causes of death (e.g., 3

individuals died of nervous system related conditions [ICD-10 classifications: G00, G03, G20–G21, G30]), we do not present results for cause-of-death analysis.

5.3.2 Measures

Ten markers were examined that have generally been included in earlier analyses using summary measures. These include indicators of cardiovascular functioning, metabolic processes and inflammation: diastolic blood pressure, systolic blood pressure, albumin, C-reactive protein (CRP), fibrinogen, glycated hemoglobin, total cholesterol, high-density lipoprotein cholesterol (HDL), and body mass index (BMI) (high: very obese, and low: underweight). Additionally, five indicators of frailty and functioning were also examined: Cystatin C (an indicator of kidney function), score of cognitive functioning, 8-foot timed walk, timed test of balance (tandem stance), and lung function (forced expiratory volume in 1 s [FEV1]/forced expiratory vital capacity [FVC]). The indicator of cognitive functioning was determined using a scale based on 26 questions. The total number of incorrectly answered questions was summed to create a cognition score, with a higher score indicating worse functioning. The questions asked included: the current date and day of the week; repeat words (e.g., apple, table, and penny) on first, second, and third trial; five monetary subtraction questions; 12 questions pertaining to story recall (six questions asked about two stories).

At-risk levels of these measures have been associated with adverse outcomes, including mortality. To examine the relationship between the latent class risks of biological and functioning indicators to mortality, we used clinical cutpoints (where available). If clinical cutpoints were not available, we attempted to distinguish the top population-based quartile and classify this as the at-risk level to dichotomize individuals into higher-risk and lower-risk levels (Table 5.1).

Based on their reported association with mortality, we considered additional variables, including: age, sex, years of education, marital status (married [includes spouse living in the household or not, as well as self-report of "living as married"] or not married [includes separated, divorced, widowed, and never married]) (Berkman 2000; Elo and Preston 1996; Idler and Benyamini 1997; Verbrugge and Wingard 1987).

5.3.3 Statistical Analysis

Latent class analysis (LCA) was conducted to classify individuals based on their biomarker and functioning profiles. LCA can be used to characterize the structure of the latent classes by determining the conditional probabilities for each of the observed variables in each of the latent classes (Clogg and Goodman 1984, 1986). Using these resultant latent classes, logistic regression models were conducted to predict mortality within 5-years of the interview when the indicators were measured. Three

Table 5.1 Cutoff points indicating higher risk for 15 biological and functioning indicators

Indicator	At-risk cutoff	%
Systolic blood pressure	> 90 mmHg	38.54
Diastolic blood pressure	> 140 mmHg	4.79
Albumin	≤ 3.9 g/dl	16.23
C-reactive protein	> 0.3 mg/dl	35.21
Fibrinogen	> 400 mg/dl	13.19
Glycated hemoglobin	≥ 6.5 %	13.08
Total cholesterol	> 240 mg/dl	33.13
High-density lipoprotein cholesterol	< 40 mg/dl	22.86
High BMI/very obese	> 35 kg/m^2	6.42
Low BMI/underweight	< 18.5 kg/m^2	1.66
Cystatin C[a]	> 1.25 mg/dl	20.16
Cognition score[a]	> 15 (of 26)	4.37
8-ft timed walk[a]	> 4.6 m/s	17.09
Timed tandem stance[a]	< 10 s	30.56
Lung function (FEV_1/FVC)[a]	< 32.89885	26.05

[a]At-risk cutoff based on top 25 % of sample distribution
BMI body mass index

models were examined: Model I adjusts for age and sex; Model II adds education (≥ high school vs < high school), marital status (dichotomus variable), and ethnicity to Model I. Model III includes self-rated health in addition to Model II covariates. For these three models, the class categorized as "no high-risk" (described below in further detail) was the latent class referent group in the analyses predicting 5-year mortality. The final model (Model IV) considers the association between a simple summary measure of allostatic load (computed by adding the total number of at-risk biological and functioning indicators [possible range 0–15] and Model III covariates. These models enable us to consider the effect of sociodemographic factors in our examination of the biological and functioning latent class risk profiles to mortality. Formally, the fully adjusted model that includes the latent class risk profiles (Model III) can be written as follows:

$$logit(\pi) = \alpha + \beta_D D_D + \beta_H H_H + \beta_L L_L$$

where D denotes demographic controls (age, sex, education, ethnicity), H denotes self-rated health, and L denotes latent class risk profiles. We account for the complex sampling design of NHANES using surveylogistic in SAS. All analyses were conducted using SAS (SAS Institute, Inc., Cary, NC), with the exception of LCA which used Latent Gold 4.5.

5.4 Results

The proportion of the US age 60+ population with high-risk levels of biomarkers and functioning indicators are reported in Table 5.1. Nearly 40 % had elevated SBP and 35 % had high CRP, while 13 % exhibited high fibrinogen levels. More than 20 % had

Table 5.2 Study sample characteristics ($N = 3{,}120$)

	Mean (SD) or %
Age	68.82 (10.76)
Male (%)	41.68
Ethnicity (%)	
Non-Hispanic white	86.04
Non-Hispanic black	7.14
Hispanic	5.35
Other	1.47
Education (%)	
< High school (<12 years)	54.25
≥ High school (≥12 years)	45.75
Married (%)	61.71
Self-reported health status (%)	
Excellent	14.79
Very good	26.18
Good	33.91
Fair	19.83
Poor	5.28
Dead after 5-year baseline (%)	13.56

high-risk (measured low) levels of HDL and 33 % had high-risk total cholesterol. A lower proportion had extreme BMI levels: 6 % were very obese and 2 % were underweight. For the measures of functioning, about 20 % had high Cystatin C levels, 31 % had low performance on the timed tandem stance, and 26 % had low lung function as indicated by FEV_1/FVC.

Table 5.2 summarizes the characteristics of the study sample. The mean age of the study population was 68.8 years, with males comprising less than half of the population (41.7 %). Overall, 61.7 % were married, and the participants had an average of 11.3 years of education (data not shown). The majority were non-Hispanic whites (86 %), with 7.1 % non-Hispanic blacks, and 5.4 % Hispanics. Five years after the initial exam, 13.6 % were no longer living.

To determine the latent class profiles that group individuals based on their biomarker and frailty profiles, we first examined all potential baseline models for the study sample. Table 5.3 shows that the 4-class model is the best baseline model based on the size of the decrease in the likelihood-ratio G^2 relative to the decline in degrees of freedom (df), which dropped substantially with the addition of each latent

Table 5.3 Comparison of baseline models from LCA for Age 60 +

No. of classes	Likelihood ratio G^2	df	AIC	BIC
2	4376.89	32736	4438.89	4626.18
3	4087.43	32720	4181.43	4465.39
4	**3912.93**	**32704**	**4038.93**	**4419.56**
5	3815.48	32688	3973.48	4450.78
6	3735.92	32672	3925.92	4499.88

Boldface type indicates the optimal model.
LCA latent class analysis, *df* degrees of freedom, *AIC* Akaike's information criteria, *BIC* Bayesian information criterion

Table 5.4 Probability estimates of high-risk biomarkers and functioning indicators of the four latent classes: No high-risk, High inflammation, High blood pressure, and High frailty

Indicator	Latent classes			
	Class 1	*Class 2*	*Class 3*	*Class 4*
	No high-risk	High inflammation	High blood pressure	High frailty
Systolic blood pressure	0.27	0.32	**1.00**	**0.46**
Diastolic blood pressure	0.02	0.00	0.31	0.02
Albumin	0.09	0.35	0.15	0.23
C-reactive protein	0.18	**0.83**	0.40	0.38
Fibrinogen	0.03	**0.44**	0.10	0.17
Glycated hemoglobin	0.06	0.29	0.16	0.17
Total cholesterol	0.32	0.33	0.40	0.30
HDL cholesterol	0.17	0.38	0.29	0.17
High BMI/obese	0.02	0.13	0.10	0.13
Low BMI/underweight	0.01	0.01	0.02	0.04
Cystatin C	0.07	0.38	0.31	**0.43**
Cognition score	0.02	0.02	0.09	0.16
Timed walk	0.07	0.13	0.10	**0.87**
Tandem stance	0.20	0.30	0.33	**0.83**
Lung function	0.23	0.33	0.30	0.27
Class probability	*0.58*	*0.19*	*0.12*	*0.11*

Note: Some factors (e.g., cholesterol measures and lung function) do not distinguish classes.
Bold indicates >0.40
N = 3,120
HDL high-density lipoprotein, *BMI* body mass index

class (up to four classes). However, when up to five classes were added, the Bayesian information criteria (BIC) increased, thereby suggesting that, for this population, the 4-class model is best (Likelihood-ratio difference = 3912.93, df = 32704).

Table 5.4 shows the probability estimates of each high-risk level of biomarkers and functioning indicators for the four latent classes. These estimates indicate the probability that an individual, who has been grouped into a given latent class, will have an at-risk level of a given biomarker. The four latent classes were termed: (1) no high-risk [low probability (≤ 0.40) of having at-risk levels for any of the indicators]; (2) high inflammation [high probability (> 0.40) of having high-risk levels of CRP after fibrinogen); (3) high blood pressure [high probability of having high SBP]; and (4) high frailty [high probability of having at-risk SBP, Cystatin C, timed walk, and tandem stand]. More than half of the study sample (58 %) were classified as no high-risk; 19 % were grouped as high inflammation; 12 % as high blood pressure; 11 % as high frailty. LCA of subgroups of ethnic categories, less than high school vs at least high school education, and marital status (married vs not married) yielded substantively similar latent classes.

Using these latent classes, we determined the odds of mortality 5-years after examination (Table 5.5). After adjusting for age and sex, individuals classified as high inflammation, high blood pressure, or high frailty, had significantly higher

Table 5.5 Odds Ratios from logistic regression models predicting 5-year mortality with latent class risk profiles (Models I-III) of biological and functioning indicators and a summary measure of allostatic load (Model IV)

Baseline variables	Model I		Model II		Model III		Model IV	
	OR	(95 % CI)	OR	(95 % CI)	OR	(95 % CI)	OR	(95 % CI)
Age (years)	1.10	(1.07–1.12)	1.09	(1.07–1.12)	1.10	(1.08–1.12)	1.09	(1.07–1.12)
Women (vs men)	0.49	(0.37–0.65)	0.47	(0.34–0.64)	0.47	(0.34–0.65)	0.46	(0.34–0.63)
≥ High School (vs. < High School)			1.03	(0.77–1.37)	1.11	(0.82–1.51)	1.11	(0.82–1.50)
Married (vs. not married)			0.88	(0.63–1.22)	0.56	(0.62–1.19)	0.83	(0.60–1.13)
Ethnicity								
NH White + Other				Reference		Reference		Reference
NH Black			1.20	(0.86–1.66)	1.08	(0.77–1.53)	1.01	(0.72–1.43)
Hispanic			0.57	(0.31–1.06)	0.53	(0.29–0.98)	0.55	(0.30–1.00)
Self-rated health								
Excellent						Reference		Reference
Very Good					1.25	(0.74–2.11)	1.19	(0.71–2.00)
Good					1.17	(0.71–1.93)	1.04	(0.63–1.71)
Fair					1.13	(0.99–1.29)	1.11	(0.98–1.27)
Poor					3.66	(1.79–7.50)	3.15	(1.58–6.30)
Latent classes								
No High-risk		Reference		Reference		Reference		
High Inflammation	2.63	(1.83–3.80)	2.62	(1.81–3.80)	2.36	(1.61–3.45)		
High Blood pressure	1.91	(1.24–2.95)	1.81	(1.16–2.82)	1.67	(1.06–2.61)		
High Frailty	2.91	(1.94–4.37)	2.85	(1.87–4.36)	2.37	(1.56–3.61)		
Summary measure of allostatic load							1.30	(1.20–1.40)

Model I includes age, sex, and latent classes.
Model II includes Model I variables plus education, marital status, and ethnicity.
Model III includes Model II variables plus self-rated health.
Model IV includes age, sex, education, marital status, ethnicity, self-rated health, and summary measure of allostatic load.

risk of 5-year mortality compared to individuals classified in the no high-risk group (Model I). The high frailty class was almost three times as likely to die after 5 years than the no high-risk class (odds ratio [OR], 95 % confidence interval [CI] = 2.91, [1.94–4.37]). Individuals in the high inflammation class were 2.6 times as likely to die than the no high-risk class, while those in the high blood pressure class were nearly two times as likely to die than the no high-risk class (OR [95 % CI] = 1.91 [1.24–2.95]). The addition of years of education, marital status, and ethnicity in Model II, did not substantially change the magnitude or significance of the latent classes to predict 5-year mortality, with the three latent classes significantly predicting mortality relative to the no high-risk class. Including self-rated health into the model (Model III) attenuated the relationship between the latent class risk profiles and mortality although the significance remained. Model IV indicates that every point increase in the summary measure of allostatic load is associated with an increase in mortality risk (OR [95 % CI] = 1.30 [1.20–1.40]).

5.5 Discussion

This study finds that older American adults can be classified into four latent class risk profiles based on ten biological markers and five indicators of functioning. The four latent classes were named based on theoretically meaningful labels: no high-risk (not high on any of the measures), high inflammation (high on fibrinogen and CRP), high blood pressure (high SBP), and high frailty (low performance on walk and tandem stance tests and high SBP and Cystatin C). Using the four designated latent classes, we found that in comparison to people in the no high-risk class, individuals grouped in the high inflammation and high frailty class were about 2.5 times as likely to die after 5 years, and those classified in the high blood pressure class were 1.7 times as likely to die after 5 years.

These findings build on previous studies that have utilized other methods to categorize biological risk, ranging from a basic summation score of elevated risk (Seeman et al. 2001) to canonical correlation analysis (Karlamangla et al. 2002, 2006) to recursive partitioning of individuals (Gruenewald et al. 2006). The latent class approach employed in this study is a unique application for biomarker classification that categorizes individuals by their individual biological and functioning profiles. This approach extends initial attempts to consider multisystem functioning and suggests the utility of the latent class approach in characterizing individuals based on their profiles of physiological dysregulation. In comparison to initial attempts to consider multiple measures using a simple equi-weight summation method (e.g., Seeman et al. 2001) and to factor analysis (as used by Sakkinen et al. 2000), the latent class approach focuses on classifying groups of individuals within a population based on similarities of their biological and functioning profiles as opposed to focusing on the inter-relationships among individual biomarkers.

An additional strength of the latent class approach is that it allows for consideration of a multi-physiological system without depending on a given outcome for

categorization. This is in contrast to the recursive partitioning method that requires an outcome measure (e.g., mortality) to categorize individuals with a given biological profile (e.g., Gruenewald et al. (2006)). Simply put, the latent class approach only uses information on the independent variables (biomarker or functioning indicators) and does not require an outcome variable in its classification process.

The approach used in the current study classifies individuals based on their system-wide underlying health status, which accounts for functioning across several physiologic subsystems without being outcome dependent. In utilizing this method, this study contributes to the current literature on population health and use of biological and functioning markers to better understand the risk profiles of some early signs of declining health in a nationally representative older population. These analyses identify differences in biomarker and functioning risk profiles among older adults and determine risk for mortality based on these classifications.

Some of our findings of increased risk of 5-year mortality among individuals having individual measures of high inflammation, high blood pressure, or high frailty have been reported in other studies. Individuals with elevated levels of inflammatory markers (including CRP and fibrinogen) have been associated with an increased risk of cardiovascular disease (Albert 2007; De Martinis et al. 2006; Kuller et al. 1996; Ridker et al. 1997; Rost et al. 2001; Tracy et al. 1997; Zakai et al. 2007), one of the leading causes of death among older US adults (Centers for Disease Control 2005). These indicators have also been predictive of both vascular and non-vascular mortality (Clarke et al. 2008) and were elevated in near-term death among older males (Jenny et al. 2007). Additionally, several population-based studies have consistently reported on the relationship between high blood pressure and increased incidence of cardiovascular disease, stroke, coronary heart disease, and mortality related to these causes (Lowe et al. 1998; National High Blood Pressure Education Program 1997; Stamler et al. 1998, 1999).

The concept of frailty, developed by geriatricians, focuses on the decline in several systems that represent increasing loss of reserves, declines in resilience, lack of energy and ability to function (Fried et al. 2001; Lunney 2003; Morley et al. 2002). Individuals classified as frail have previously been noted to have poorer health and to be at greater risk of mortality compared to non-frail individuals (Cawthon et al. 2007; Mitnitski et al. 2005). Typically included among indicators of frailty, and as examined here, are markers of system functioning (e.g., cognitive status) and performance measures (e.g., timed walk test and timed tandem stance) (Crimmins et al. 2010; Rothman et al. 2008). Understanding the links between these various dimensions and risk profiles of health and mortality will provide us with an improved understanding of the processes associated with aging and mortality.

Overall, this study has several strengths. First, it uses a nationally representative sample of the US population to investigate the relationship among various biomarkers to one another, as well as to mortality. Second, it utilizes mortality follow up data obtained through a reliable data source: the National Death Index. Third, this is the first study to our knowledge that methodologically examines the relationship of both biomarkers and indicators of functioning using the latent class approach.

Despite its strengths, our study also had limitations. For instance, we were limited to the use of logit models to investigate the relationship between the latent classes and 5-year mortality given that we only had information on survival status. This did not include date of death information, so we were unable to conduct more sophisticated analyses to model survival.

The latent class approach to classifying individuals based on their biological and functioning profiles was found to significantly predict 5-year mortality. More specifically, individuals with profiles that include high-risk levels of inflammation, blood pressure, and frailty were more likely to die than individuals classified as no high-risk. This methodological approach to using multiple indicators obtained at one time point seems an appropriate means to classifying individuals based on multiple biological and functioning indicators that represent functioning across several physiological systems. Our findings also suggest the importance of using these indicators to evaluate older adults at high-risk for these markers, in order to improve the health and years lived among older adults.

Acknowledgments This work was supported in part by the US National Institute on Aging Grants T32AG0037 and P30 AG17265. Merril Silverstein and Wonho Lee provided helpful suggestions on a previous draft of this manuscript.

Appendix

Table A.1 Percent with at-risk cutoff points for 15 biological and functioning indicators by marital status, education level, and ethnicity

Indicator		Marital status		Education		Ethnicity		
	At-risk cutoff	Married	Not Married	< High school	≥ High school	NH white[b]	NH black	Hispanic
Systolic blood pressure	> 90 mmHg	40.82	49.04	46.6	41.02	42.32	48.69	45.43
Diastolic blood pressure	> 140 mmHg	6.39	5.59	6.98	4.91	4.53	10.86	6.24
Albumin	≤ 3.9 g/dl	15.75	20.13	18.27	16.48	15.72	24.34	16.55
C-reactive protein	> 0.3 mg/dl	36.83	39.46	39.92	35.62	35.98	45.71	36.72
Fibrinogen	> 400 mg/dl	14.85	16.53	16.85	13.96	14.02	19.79	16.11
Glycated hemoglobin	≥ 6.5 %	17.3	16.21	20.11	13.04	11.89	25.39	23.22
Total cholesterol	> 240 mg/dl	29.91	33.71	30.87	32.12	31.82	33.98	28.59
High-density lipoprotein cholesterol	< 40 mg/dl	27.78	16.53	24.9	21.46	24.2	14.19	28.16
High BMI/very obese	> 35 kg/m^2	6.12	7.19	8.10	4.70	5.28	10.16	7.26
Low BMI/underweight	< 18.5 kg/m^2	0.69	2.80	1.24	1.68	1.76	1.58	0.87
Cystatin C[a]	> 1.25 mg/dl	18.79	27.56	24.36	19.78	26.6	17.16	14.66
Cognition score[a]	> 15 (of 26)	6.65	11.5	13.01	3.02	5.49	14.19	12.34
8-ft timed walk[a]	> 4.6 m/s	18.47	32.67	31.11	15.85	19.94	29.42	31.2
Time tandem stance[a]	< 10 s	29.54	44.49	40.04	30.01	37.05	33.63	32.95
Lung function[a]	< 32.89885	25.12	22.92	24.72	23.63	27.61	21.72	17.13

BMI body mass index, *NH* non-hispanic

[a]Based on top 25 % sample distribution

[b]Includes "Other" ethnic groups not classified as NH White, NH Black, or Hispanic

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