Published in final edited form as:

J Am Geriatr Soc. 2008 September ; 56(9): 1698–1703. doi:10.1111/j.1532-5415.2008.01858.x.

Physiological Complexity Underlying Heart Rate Dynamics and Frailty Status in Community-Dwelling Older Women

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Abstract

OBJECTIVES—To assess whether less physiological complexity underlying regulation of heart rate dynamics, as indicated by lower approximate entropy for heart rate (ApEn_{HR}), is associated with frailty. For supporting validity, relationships between frailty and traditional linear indices of heart rate variability (HRV) were also assessed.

DESIGN—Cross-sectional.

SETTING—Women's Health and Aging Study I, a community-based observational study, 1992 to 1995.

PARTICIPANTS—Subset of 389 community-dwelling women aged years and older with moderate to severe disability with ApEn_{HR} data (convenience sampling).

MEASUREMENTS—Electrocardiographic Holter recordings obtained over 2- to 3-hour periods were processed for ApEn_{HR} and HRV measures. ApEn_{HR} is a nonlinear statistic that quantifies the regularity of heart rate fluctuations over time. Lower ApEn_{HR} is characteristic of heart rate time series containing a high proportion of repetitive patterns. Frailty was defined according to validated phenotype criteria.

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Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this manuscript.

Author Contributions: Chaves, Varadhan, and Lipsitz: concept and design, analysis and interpretation of data, manuscript preparation. Fried and Guralnik: concept and design, acquisition of subjects and data, analysis and interpretation of data, manuscript preparation. Stein, Windham, and Tian: analysis and interpretation of data, manuscript preparation. Fleisher: acquisition of data, analysis and interpretation of data, manuscript preparation.

RESULTS—Median ApEn_{HR} was lower in frail than in nonfrail subjects ($P = .02$). Lower ApEn_{HR} (top quartile) was associated with lower likelihood of frailty than higher ApEn_{HR} (bottom three quartiles) (odds ratio = 0.47, 95% confidence interval = 0.26–0.86), even after adjustment for major confounders. Frailty was consistently associated with lower HRV as assessed using time- and frequency-domain indices.

CONCLUSION—This study supports the notion that less physiological complexity marks frailty and provides an empirical basis to the concept of frailty as a syndrome of homeostatic impairment. Future research will determine whether noninvasive measures of physiological complexity underlying heart rate dynamics might be useful for screening and monitoring of clinical vulnerability in older adults.

Keywords

frailty; approximate entropy; heart rate variability; elderly; physiological complexity

Substantial heterogeneity in clinical resilience is observed in community-dwelling older adults. In the face of acute and chronic stressors, there are those who are vulnerable and most prone to developing health complications at one end of the clinical spectrum and those who are relatively robust at the other end. The term “frailty” is often used to describe the clinical status of people who are most vulnerable and at high risk for major adverse outcomes, including accelerated functional decline, physical disability, diminished clinical recovery ability, and mortality.¹ Better understanding of the still-elusive mechanisms that contribute to the pathogenesis of frailty in older adults, a major clinical and public health concern, may prove useful for the development of novel preventive opportunities.

Physiological impairments may accumulate over time as a consequence of clinical and subclinical diseases, adverse exposures (e.g., health habits, environment), genetic factors, and the ill-defined aging process. Accumulation of physiological impairments may result in deterioration of complex, dynamic interactions across multiple regulatory systems that fine-tune homeostatic adaptive responses to stressors. Conceptually, deterioration of this complex network of interacting physiological signals, which can be thought of as a reduction in “physiological complexity,” may compromise the capacity to mount compensatory physiological adaptations in response to stressors and lead to greater clinical vulnerability—or frailty status—in older adults,^{2,3} but empirical data characterizing the direct relationship between “physiological complexity” and frailty status in older adults remain scarce. Recent advances in frailty measurement and the development of measures that, albeit indirectly, may be used to quantify “physiological complexity” now offer an opportunity to examine such a relationship.

Heart rate variability (HRV) refers to natural fluctuations in the interval between normal heartbeats that occurs while individuals rest or go about their everyday activities. These fluctuations, which are primarily modulated by autonomic nervous system inputs to the sinus node, reflect the continuous exchange of regulatory signals across the physiological systems involved in the maintenance of cardiovascular homeostasis. Approximate entropy for a heart rate time series (ApEn_{HR})⁴ is a statistic that quantifies the regularity (or degree of predictability) of heart rate fluctuations over time. A time series containing a high proportion of repetitive, similar patterns will have a small ApEn_{HR} . Conversely, greater fluctuation corresponds to higher ApEn_{HR} values. It has been proposed that less heart rate fluctuation (i.e., greater regularity, lower ApEn_{HR}) may serve as a surrogate marker for less physiological complexity,³ although major caveats should be considered. For example, greater fluctuations in heart rate due to random fluctuations or marked arrhythmia result in higher ApEn_{HR} without corresponding to a higher level of physiological complexity, although lower ApEn_{HR} always corresponds to a loss in complexity. The reader is referred to excellent discussions addressing

the usefulness and limitations of ApEn_{HR} as a nonlinear measure of physiological complexity.^{5–7} In support of the use of ApEn_{HR} as a surrogate measure of physiological health are studies that have documented associations between lower heart rate ApEn_{HR} and older age,^{8–11} greater morbidity,¹² and greater mortality.¹³

The goal of this cross-sectional study was to test in older adults the hypothesis of a link between frailty and loss of physiological complexity, as indicated by low ApEn_{HR} . Additionally, for supporting validity, the relationship between frailty status and traditional time- and frequency-domain indices of HRV was examined. Positively correlated with nonlinear measures of complexity underlying heart rate dynamics, these linear indices are associated with health outcomes. For example, low levels of traditional time- and frequency-domain HRV indices, which reflect autonomic dysfunction, have been consistently shown to be associated with major frailty-related risk factors and outcomes.^{14–18} In this context, whether low levels of traditional HRV indices were associated with frailty was assessed.

METHODS

Study Design

This was a cross-sectional study involving secondary analysis of baseline data from a subset of older women in the Women's Health and Aging Study (WHAS), Baltimore, Maryland, 1992 to 1995. WHAS I was originally designed as an observational study aimed at the investigation of the epidemiology of disability progression in 1,002 non-institutionalized women aged 65 and older who had moderate to severe physical disability at the beginning of the study.¹⁹ Ambulatory electrocardiographic (ECG) Holter recordings over a 2- to 3-hour period were obtained on 812 subjects during standardized in-home evaluations. As part of a previous pilot initiative primarily focused on ApEn_{HR} assessment, and using convenience sampling, 389 recordings were processed for ApEn_{HR} . Holter tapes were selected based on calendar time (i.e., all tapes collected between April 1993 and November 1994). There were no major differences between WHAS I subjects in the ApEn_{HR} subset and the group without ApEn_{HR} data with regard to key parameters, including frailty status, mobility disability, and cardiovascular disease (CVD) (data not shown). The Johns Hopkins Medical Institutions institutional review board approved the study procedures.

Frailty

Frailty was defined according to previously validated criteria^{1,20} as the presence of three or more of the five clinical characteristics: shrinking (having lost >10% of one's weight since age 60; slowness (bottom 20th percentile of 4-m usual walking speed stratified according to sex and height); weakness (bottom 20th percentile of maximal grip strength measured using a Jamar handheld isometric dynamometer stratified according to sex and body mass index); exhaustion (self-report of feeling unusually tired or weak most or all of the time in the previous month or scoring ≤ 3 on a visual analog scale assessing usual energy level (0 = no energy to 10 = most energy you have ever had)); and low energy expenditure (bottom 20th percentile of total physical activity in the previous 2 weeks, according to self-report). These characteristics can be thought of as a critical mass of clinical manifestations in a "vicious cycle" of dysregulated physiology.¹

Holter Monitoring

Two-channel continuous ECG recordings over a 2- to 3-hour period were obtained on 812 subjects using a calibrated analog Holter device with a temporal resolution of 120 Hz (SpaceLabs model 90205, Redmond, WA). Holter recording conditions varied as study participants underwent WHAS I procedures that required them to assume diverse positions (e.g., lying, sitting, standing) and to perform physical tasks, including walking, isometric

exercise (e.g., grip strength assessment), and other tests.¹⁹ Analog tape recordings were digitized and processed using a computerized analysis system (SpaceLabs FT 2000). After the scanner automatically detected and labeled all QRS complexes, files were reviewed in detail and edited by an investigator (LAF) to ensure that only normal-to-normal (N-N) intervals were included in the time domain, frequency domain, and nonlinear HRV analysis.

ApEn_{HR} measures the logarithmic likelihood that runs of patterns that are close (within r) for m continuous observations remain close on next incremental comparisons. It was calculated according to methods previously described.¹² For this study, ApEn_{HR} was calculated using $m = 2$ and $r = 10$ ms (20% of the average standard deviation of the HR series).

Traditional HRV indices were obtained according to conventional methods.²¹ The following time-domain indices of HRV were calculated: the standard deviation of all N-N intervals (SDNN), the standard deviation of the average N-N over 5-minute periods (SDANN), and the square root of the mean squared differences of successive NN intervals (rMSSD). Frequency domain HRV indices were derived from power spectral analysis using the fast Fourier method, which partitioned the variability in heart rate into four frequency bands: very low frequency (VLF; <0.04 hertz), which reflects parasympathetic modulation of heart rate and is influenced by the rennin-angiotensin system; low frequency (LF; 0.04–0.15 hertz), which reflects sympathetic and parasympathetic modulation; and high frequency (HF; 0.15–0.4 hertz), which primarily reflects heart rate fluctuations due to parasympathetically mediated respiratory sinus arrhythmia, although non-respiratory sinus arrhythmia (erratic rhythm) can also influence it.²² Additionally, total power (TP), the overall heart rate variance across all frequency bands, and the ratio LF:HF, which has been proposed as a marker of sympathetic/parasympathetic balance, were calculated. Time- and frequency-domain indices were available for 309 and 301 subjects, respectively, who were part of the ApEn_{HR} subset. Potential reasons for why time- and frequency-domain indices were not available for all subjects in the ApEn_{HR} subset were not documented. There were no major differences in relevant parameters, including age, frailty status, and self-reported health between ApEn_{HR} subset subjects with and without time- or frequency-domain data.

Other Independent Variables

Data collected as part of the baseline WHAS I in-home evaluations used in this analysis included demographics (age and race), adjudicated diagnosis of definite disease¹⁹ (diabetes mellitus, coronary heart disease (angina pectoris or myocardial infarction), and congestive heart failure), surrogate measures of subclinical cardiovascular disease (CVD)²³ (left ventricular hypertrophy on ECG and ankle-brachial index (the ratio of systolic blood pressure in the posterior tibial artery to the systolic blood pressure in the brachial artery)), presence of depressive symptoms according to the Geriatric Depression Scale (GDS), short version,²⁴ history of fall within the previous 12 months (yes vs no), prevalent use of beta-blockers or antidepressants based on review of all medications study participants had at home, Short Physical Performance Battery (SPPB) score, an objective performance-based assessment of lower-extremity function²⁵ that combines the results of three tests: time to walk 4 m at usual pace, time to rise from a chair five times as rapidly as possible with arms crossed in front of chest, and ability to hold balance in different standing positions (scores range from 0 to 12, with scores 10 to 12 indicating best performance), Mini-Mental State Examination (MMSE),²⁶ and self-rated health status (excellent, very good, good, fair, or poor).

Analysis

Nonparametric Wilcoxon rank-sum testing was used to assess equality of ApEn_{HR} medians according to selected characteristics. Multiple logistic regression models estimated the likelihood of being frail as a function of having higher (top quartile) versus lower ApEn_{HR}

(other 3 quartiles), adjusting for age (Model 1), age plus diseases (Model 2), and age plus diseases plus health and functional status (Model 3). Diseases entered in Model 2, which were selected a priori, included those shown in the literature to be associated with autonomic dysfunction. In Model 2, as an attempt to minimize confounding effects by prevalent subclinical CVD, an index that combined the two measures included in the Cardiovascular Health Study subclinical CVD index²³ that were available for the analysis (presence of left ventricular hypertrophy and ankle-brachial index <0.9) were adjusted for. Model 3 also adjusted for comorbidity burden indices that, although linked to frailty, are conceptually different from it.¹ These indices were objective, performance-based measures of physical (SPPB) and cognitive (MMSE) function and an important subjective index of overall health status (self-rated health). Frequency bars and chi-square statistics were used to assess the distribution of frailty status according to HRV status (lower (bottom quartile) vs higher (top 3 quartiles)). The ratio LF:HF and ApEn_{HR} were classified differently (lower (bottom 3 quartiles) vs higher (top quartile)). This was done based on the different threshold pattern observed in the relationship between frailty status and LF:HF during preliminary analysis. In all analyses, $P < .05$ was considered to statistically significant. Stata 9.0 was used for analysis (Stata Corp., College Station, TX).

RESULTS

Characteristics of study participants are shown in Table 1. More than two-thirds were aged 75 and older. Although most were white, there was a substantial proportion (>30%) of African Americans; 33.4% ($n = 130$) were classified as frail. Distributions of disease and functional indicators reflected the fact that the parent study that served as the basis for this analytical sample recruited from among the most disabled population of older women living in the community. Median ApEn_{HR} was lower in frail than in nonfrail subjects (0.90 vs 0.96, $P = .03$), but it was not associated with age in these older women. Median ApEn_{HR} was also observed to be statistically significantly ($P < .05$) lower in white subjects, subjects with diabetes mellitus, beta-blocker users, antidepressant users, and those with a history of fall. Other characteristics associated with lower median ApEn_{HR}, although in a statistically nonsignificant fashion, were prevalent coronary heart disease, prevalent Parkinson's disease, greater depressive symptom burden, and low MMSE score.

Preliminary analysis involved the construction of scatterplot graphs along with the use of smoothing techniques for the visualization of the relationship between the probability of frailty as a function of ApEn_{HR} levels. That analysis revealed a threshold pattern (within the top ApEn_{HR} quartile, there was a monotonous decrease in the probability of frailty with increasing ApEn_{HR} levels (data not shown)). Based on this pattern, it was decided to classify ApEn_{HR} as higher (top quartile; ≥ 1.8) or lower (bottom 3 quartiles). Table 2 displays multivariate logistic regression results. Lower ApEn_{HR} was associated with significantly higher likelihood of being frail in models that adjusted for age (Model 1); age, race, and disease-related covariates (Model 2); and all covariates in Model 2 plus objective performance-based measures of physical and cognitive function, and subjective perception of overall health status (Model 3). For example, even after the comprehensive adjustment done in Model 3, those who had lower ApEn_{HR} were twice as likely to be classified as frail as those without lower ApEn_{HR} (odds ratio (OR) = 1.99, 95% confidence interval (CI) = 1.1–3.7; $P = .03$). Further adjustment for use of antidepressants in Model 3 did not substantially change the association between ApEn_{HR} and frailty (data not shown).

Figure 1 shows bivariate analysis results. In addition to being associated with lower ApEn_{HR}, frailty was also consistently associated with lower levels of traditional time- and frequency-domain indices of HRV. Specifically, all indices of lower HRV were associated

with a higher probability of frailty ($P<.05$), with the exception of HF and rMSSD, two highly correlated indices (the Pearson correlation coefficient was 0.80).

DISCUSSION

This study documented a direct link between frailty and less physiological complexity underlying heart rate dynamics, as indicated by lower $ApEn_{HR}$, in community-dwelling older women. These data offer empirical support for the hypothesis that decay in dynamic interactions between physiological systems involved in the homeostatic regulation of vital processes such as heart rate may contribute to frailty.^{2,3}

The observed relationship between lower $ApEn_{HR}$ and frailty was consistent with findings of associations of lower levels of traditional linear time- and frequency-domain indices of HRV with frailty. It was also consistent with previous results linking lower $ApEn_{HR}$ with older age.^{8,9} Additionally, it was consistent with previously documented associations between lower linear HRV indices with aging and disease,¹⁵ cognitive impairment,²⁷ and mortality in older adults.^{16,28,29}

Frailty was associated with reduction in all but one (HF variability) of the traditional HRV indices studied here, but this was not truly surprising. Mixed findings have been reported with regard to associations between frailty-related clinical parameters^{14,28} and low HF variability or low variability measured using traditional short-term HRV indices highly correlated with HF. The latter include the percentage of differences between successive NN intervals that are greater than 50 milliseconds (pNN50), and the rMSSD.³⁰ Rather than reflecting a true lack of difference in vagal tone between frail and nonfrail older subjects, the observed lack of association between HF variability and frailty could reflect confounding effects of erratic rhythms not readily detectable on Holter scans that short-term HRV indices capture. This is consistent with what has been previously proposed to explain findings of an association between greater short-term HRV and higher mortality.¹⁶

Assessment of independent relationships between $ApEn_{HR}$ and clinical correlates other than frailty status was beyond the scope of these analyses. Nonetheless, a number of bivariate associations between $ApEn_{HR}$ and medical parameters were observed in a manner consistent with what could be expected based on previous literature findings. Lower median $ApEn_{HR}$ was positively associated with diabetes mellitus, history of falls, and use of antidepressants and negatively correlated with use of beta-blockers. It is likely that lack of statistically significant bivariate associations between low $ApEn_{HR}$ and coronary heart disease, higher number of depressive symptoms, congestive heart failure, self-reported health status, and performance on objective tests of mobility function reflect limited distribution variability due to selective recruitment of disabled older adults into WHAS I, as well as the potential effect of survival bias and confounders.

These findings should be interpreted in light of important limitations. Analyses were cross-sectional, precluding assessment of temporal relationships. Although $ApEn_{HR}$ may be used as a surrogate marker for physiological complexity underlying control of heart rate dynamics, arrhythmia (e.g., atrial fibrillation) and random “noise” may result in greater $ApEn_{HR}$ that does not constitute greater physiological complexity. To minimize the potential effect of this pitfall on study inferences, ECG recordings were closely inspected for exclusion of arrhythmias. Additionally, consistency of $ApEn_{HR}$ findings with those observed between reduced traditional time and frequency domain HRV indices and frailty provide content validity support for the $ApEn_{HR}$ findings.

In summary, this study supports the notion that less physiological complexity marks frailty and provides an empirical basis for the concept of frailty as a syndrome of homeostatic

impairment. As next steps in this line of investigation, whether noninvasive evaluation of physiological complexity underlying heart rate dynamics might be useful in the screening and identification of clinical vulnerability in older adults will be assessed. Also, whether these measures could be useful for the monitoring of changes in physiological complexity over time, which would be of interest for evaluation of frailty interventions, will be explored.

Acknowledgments

This research supported by Johns Hopkins Older Americans Independence Center—National Institute on Aging (NIA) Grant P30 AG021334; National Institutes of Health (NIH)-NIA Grant R37 AG19905; the Intramural Research Program, NIA, NIH; and NIA Grant AG025037.

Sponsor's Role: Drs. Guralnik and Windham are investigators affiliated with the NIA, which sponsored this study. Their scientific contribution is noted above.

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Figure 1.

Frailty status distribution according to the presence of lower versus higher heart rate variability (HRV). The percentage of study participants classified as frail was consistently higher in the low HRV categories for all but high frequency (HF). *P*-values refer to the comparison of frailty status between lower and higher HRV categories. Lower versus higher was defined as the bottom three quartiles versus the top quartile, for the ratio low frequency (LF):HF and approximate entropy for heart rate (ApEn_{HR}), based on thresholds observed during preliminary data analysis. For all other indices, levels in the bottom quartile were considered to be lower, and levels within the top three quartiles were classified as higher. NN = normal to normal. HRV indices assessed included the following: SDNN, standard deviation of all NN intervals; SDANN, standard deviation of the average NN interval over 5-minute periods; rMSSD, square root of the mean squared differences of successive NN intervals; TP, total power; VLF, very low frequency.

Table 1

Characteristics of Study Population and Distribution of Heart Rate–Based Approximate Entropy According to Selected Characteristics

Characteristic	N (%) [*]	Heart Rate–Based Approximate Entropy Median [25th–75th Percentile]	P-Value
Frailty			
No	259 (60.6)	0.96 [0.68–1.2]	.03
Yes	130 (33.4)	0.90 [0.60–1.1]	
Demographics			
Age			
65–74	122 (31.4)	0.92 [0.61–1.2]	.49
75–95	267 (68.6)	0.94 [0.71–1.2]	
Race			
Nonwhite	117 (30.1)	1.1 [0.76–1.3]	.002
White	272 (69.9)	0.90 [0.63–1.1]	
Disease-related			
Coronary heart disease			
No	265 (68.1)	0.96 [0.72–1.2]	.10
Yes	124 (31.9)	0.86 [0.60–1.2]	
Congestive heart failure			
No	354 (91.0)	0.94 [0.65–1.2]	.39
Yes	35 (9.0)	0.95 [0.74–1.3]	
Diabetes mellitus			
No	323 (83.9)	0.94 [0.71–1.2]	.04
Yes	66 (17.0)	0.82 [0.53–1.1]	
Stroke			
No	362 (93.1)	0.94 [0.65–1.2]	.79
Yes	27 (6.9)	0.92 [0.68–1.2]	
Parkinson's disease			
No	383 (98.5)	0.94 [0.66–1.2]	.24
Yes	6 (1.5)	0.76 [0.37–.96]	
Beta-blocker use			
No	308 (79.2)	0.91 [0.64–1.1]	.01
Yes	81 (20.8)	1.1 [0.76–1.3]	
Antidepressant use			
No	359 (92.3)	0.94 [0.69–1.2]	.006
Yes	30 (7.7)	0.70 [0.40–1.0]	
Fall in previous year			
No	260 (67.0)	0.96 [0.71–1.2]	.04
Yes	128 (33.0)	0.89 [0.60–1.1]	
Geriatric Depression Scale score			
<5	304 (78.2)	0.95 [0.69–1.2]	.09
≥5	85 (21.9)	0.87 [0.61–1.1]	

Characteristic	N (%) [*]	Heart Rate-Based Approximate Entropy Median [25th–75th Percentile]	P-Value
Functional/health status			
Short Physical Performance Battery			
10–12	313 (80.7)	0.98 [0.62–1.2]	.45
≤9	75 (19.3)	0.93 [0.66–1.2]	
Mini-Mental State Examination			
≥24	321 (82.5)	0.95 [0.68–1.2]	.05
<23	68 (17.5)	0.89 [0.61–1.1]	
Self-rated health			
Excellent or very good	73 (18.9)	0.93 [0.65–1.1]	.76
Good, fair, or poor	313 (81.1)	0.94 [0.65–1.2]	

* Some percentages do not total 100 because of rounding.

Table 2

Multivariate Logistic Regression Models Estimating the Likelihood of Being Frail Associated with Lower (Bottom 3 Quartiles) Versus Higher (Top Quartile) Heart Rate-Based Approximate Entropy (ApEn_{HR}) Controlling for Different Sets of Covariates

	Model 1	Model 2	Model 3
Variable	Odds Ratio (95% Confidence Interval) P-Value		
Low ApEn _{HR}	1.9 (1.1–3.2) .03	2.1 (1.2–3.8) .02	2.0 (1.1–3.7) .03
Age (5-year increments)	1.6 (1.4–1.8) <.001	1.7 (1.4–2.0) <.001	1.5 (1.3–1.8) <.001
Race (nonwhite vs white)		1.7 (.97–2.9) .07	1.2 (.66–2.2) .54
Prevalent coronary heart disease (yes vs no)		1.3 (.75–2.1) .39	1.1 (.62–1.8) .83
Prevalent congestive heart failure (yes vs no)		2.3 (1.0–5.1) .05	2.4 (1.0–5.5) .04
Prevalent diabetes (yes vs no)		1.8 (.95–3.4) .07	1.8 (.95–3.4) .07
Ankle-brachial index <0.9 or left ventricular hypertrophy			
Yes vs no		1.4 (.82–2.2) .23	1.3 (.77–2.1) .35
Missing vs no		1.8 (.59–5.7) .30	1.7 (.53–5.2) .38
Use of beta-blocker (yes vs no)		1.0 (.56–1.9) .93	1.1 (.58–2.1) .79
Geriatric Depression Scale score ≥5 vs <5		2.8 (1.6–5.0) <.001	2.3 (1.3–4.2) .005
Fall in previous year (yes vs no)		1.7 (1.0–2.8) .04	1.7 (1.0–2.9) .04
SPPB score (≤9 vs 10–12)			3.6 (1.4–9.3) .008
MMSE (1-point decrement)			1.1 (.97–1.2) .18
Health status (poor, fair, or good vs very good or excellent)			2.0 (.98–3.9) .06

Note: Model 1 included only the covariates low ApEn_{HR} and age. Model 2 included all covariates listed in the Variable column with the exception of Short Physical Performance Battery (SPPB) score, Mini-Mental State Examination (MMSE), and health status. Model 3 included all covariates listed in the Variable column.