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Derivation of a measure of physiological multisystem dysregulation: Results from WHAS and Health ABC

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Abstract

Introduction.—Multifactorial biological processes underpin dysregulation over several individual physiological systems. However, it is challenging to characterize and model this multisystemic dysregulation and its relationship with individual physiologic systems. We operationalized a theory-driven measure of multisystem dysregulation and empirically tested for measurement differences by key characteristics.

Methods.—We used the Women's Health and Aging Studies (WHAS) I and II (N=649), and the Health ABC study (N=1,515). Twelve biomarkers representing multiple systems including stress response (e.g., inflammation), endocrine system, and energy regulation were identified. A series of

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Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

confirmatory factor analyses (CFA) were conducted to evaluate the interplay between physiological systems and underlying multisystem dysregulation. We evaluated convergent criterion validity of a score for multisystem dysregulation against the physical frailty phenotype, and predictive criterion validity with incidence of walking difficulty and mortality.

Results.—A bifactor CFA, a model in which dysregulation of individual systems proceeds independently of generalized dysregulation, fit data well in WHAS (RMSEA: 0.019; CFI: 0.977; TLI: 0.961) and Health ABC (RMSEA: 0.047; CFI: 0.874; TLI: 0.787). The general dysregulation factor was associated with frailty (OR: 2.2, 95% CI: 1.4, 3.5), and elevated risk of incident walking difficulty and mortality. Findings were replicated in Health ABC.

Discussion.—Biomarker data from two epidemiologic studies support the construct of multisystem physiological dysregulation. Results further suggest system-specific and system-wide processes have unique and non-overlapping contributions to dysregulation in biological markers.

Keywords

biomarkers; frailty; psychometrics

Introduction

Dysregulation in a single physiological system can lead to recognized, diagnosable diseases such as hypo or hyperthyroidism, which in turn can result in adverse health conditions such as atrial fibrillation (1). While individual biomarkers, and sets thereof, can be used to characterize dysregulation in specific physiological systems (2–6), it is increasingly recognized that dysregulation in tandem across a constellation of physiological systems may have deleterious health effects, as well as implications for the development of aging phenotypes (7). Dysregulation across multiple systems, measurable using multiple biomarkers from different systems, is thought to result from a loss of complexity of interactions among individual physiological systems in addition to their own deterioration (8–9). Multisystemic physiological dysregulation may then lead to the body's inability to adequately compensate for stressors. Indeed, studies have demonstrated individual biomarkers interact with other biomarkers in complex physiological networks to maintain homeostasis (10–11). Research over the past 20 years has coalesced around the notion of physical frailty as a manifestation of multisystem dysregulation at the physiological level (6,12).

This study's motivating premise is that multifactorial biological processes underpin dysregulation which spans multiple physiological systems; the question is, how should this dysregulation be modeled? To drive research and development of prevention and treatment regimens, it is important to characterize and to empirically model the underlying, potentially multifactorial, mechanisms by which dysregulation in biomarkers across multiple body systems are connected. How best to juxtapose multisystemic physiological dysregulation and individual dysregulated systems remains understudied. (1) Does an overarching process of general dysregulation manifest directly in individual component physiological systems, which in turn results in dysregulation of biomarkers specific to the individual component systems (described in panel B of Figure 1)? (2) Alternatively, is there a major component of

physiological dysregulation unique to individual systems, independent of the overarching multisystem dysregulation, which also contributes to variation in dysregulated levels of biomarkers (described in panel C of Figure 1)? (3) Or, is there no need to account for component systems when empirically representing multisystemic physiological dysregulation (described in panel A of Figure 1)?

In this study, we evaluated these contrasting hypotheses by fitting several alternative theory-driven structural equation models of biomarkers representing multiple physiological systems. Based on theory, previous research, and data availability, we chose to study physiological systems related to stress response (e.g., inflammation), those related to interconnections among endocrine systems, and energy and nutrient metabolism. We empirically evaluated criterion validity of a resulting measure of multisystemic dysregulation, derived from the best-fitting structural equation model, using clinical frailty, time to incident mobility difficulty, and time to death. We further tested for measurement differences in multisystem dysregulation by background demographic characteristics (age, race) and study membership. We developed models and replicated findings using two cohorts.

Materials and Methods

We used data from the Women's Health and Aging Studies (WHAS) I and II, as well as the Health, Aging and Body Composition (Health ABC) study. The WHAS studies are population-based observational studies that initially recruited from Medicare eligibility lists in Baltimore, Maryland (13–14). They are complementary in that WHAS I recruited N=1,002 women who represented the one third most disabled women living in the community, while WHAS II recruited N=436 women who represented the two thirds least disabled. Exclusion criteria for WHAS I comprised of Mini Mental State Examination (MMSE)<19 (15) and self-reported difficulties in less than two of four functional domains related to mobility, upper extremity function, household management, and self-care. Exclusion criteria for WHAS II comprised of MMSE<24 and self-reported difficulty in more than one aforementioned functional domain. At baseline, WHAS I recruited women aged 65 years and older, while WHAS II recruited women who were 70 to 79 years of age. WHAS I participants were examined in their homes at baseline and semi-annually for up to 3 years. WHAS II participants were examined in a clinic setting at baseline and 1.5, 3, 6, 7.5, and 9 years thereafter. Further details are available elsewhere (13,16–17). Trained phlebotomists collected nonfasting blood samples, which were processed using standardized protocols at the Core Genetics Laboratory of the Johns Hopkins School of Medicine, then shipped to Quest Diagnostics the same day for assays.

Health ABC is a longitudinal study of body composition and functional changes among older adult men and women recruited from Medicare beneficiary lists and the community. Enrollment criteria included 70–79 years of age, no reported ADL difficulty, and no difficulties walking a quarter mile or climbing steps. Additional details of the study's recruitment and composition are available elsewhere (17).

WHAS I and II were comprised of women only, so in primary analyses we excluded men from Health ABC. Participants in WHAS II and Health ABC were aged 70–79 years at baseline, so we excluded participants who were younger than 70 years old or over 79 years old at baseline in WHAS I. We further excluded participants with missing data on all biomarkers. Final sample sizes were N=265 women in WHAS I, N=384 women in WHAS II, and N=1,515 women in Health ABC.

All participants provided written informed consent for each study, and the studies were approved by appropriate Institutional Review Boards.

Variables

Direct examination of physiological systems in older adults can be challenging, however biomarkers measurable in serum can provide insights, albeit gross and error-prone, into physiological function. We used such biomarkers representing physiological systems related to stress response (e.g., inflammation), interconnections among endocrine systems, and energy and nutrient metabolism. Because frailty has been characterized as resulting from multisystemic physiological dysregulation, research on the former as a manifestation of the latter guided our selection of biomarkers for each system (6,12). Markers of chronic inflammatory pathway activation, including elevated interleukin-6 (IL-6) (5,18–19), c-reactive protein (CRP) (5,20–21), and TNF-alpha receptor 1 (22), have been associated with frailty status via catabolic effects on muscles both individually (23) and collectively (24). Additionally, high levels of white blood cells (19,25), in particular monocytes (25), have been associated with frailty in the WHAS studies. Because TNF-alpha receptor 1 was assayed and available in Health ABC but not in WHAS I and II, we did not include it in the present study. We also considered two ubiquitous metabolic markers, HDL cholesterol and albumin, for this study (26). These markers are often considered as nutritional variables. However, their levels are more likely to be influenced by underlying metabolic processes such as chronic inflammation rather than nutritional intake per se in population studies of older adults (27–28). Hormones in the endocrine system implicated in frailty onset and progression include low levels of estradiol (29), testosterone (29–31), insulin growth factor (IGF) (18,25), thyroid stimulating hormone (TSH) (32), and DHEA-S (18,33). Biomarkers related to glucose metabolism include fasting levels of glucose and HbA1c (34–35).

For the present study, from the assayed biomarkers we identified 12 serum biomarkers of stress response, endocrine systems, and energy metabolism that were measured in a comparable way across the cohorts (Supplemental Table 1). All biomarkers were assayed in serum using protocols specific to the WHAS and Health ABC studies, and were prospectively collected within two years of each other in each study. Cutoffs to define abnormal levels of each biomarker, provided in Supplemental Table 1, were based either on widely accepted criteria or, when no established absolute cutoffs were available, on top/bottom tertiles (12). Dysregulated biomarker levels were coded as 1 and normal levels were coded as 0 (in some cases this was the upper tertile, and in other instances lower tertile). We selected a bidirectional cutoff for free testosterone because both low and high levels in women can have adverse consequences. In a sensitivity check, we reran analyses using cutoffs based on deciles instead of tertiles. We chose to use cutoffs for biomarkers to more

clearly articulate the indicators as markers of abnormality or dysregulation, rather than as continuous physiologic measures that assume dysregulation may be due to deviation in either direction from average. While that is a reasonable alternative approach (e.g., 11), bidirectional dysregulation might not make sense for all systems important in frailty and aging. For example, high levels of pro-inflammatory markers such as IL-6 and TNF-alpha exhibit unidirectional dysregulation. It is unreasonable to assume that both low and high values indicate dysregulation; this is why the body has both pro- and anti-inflammatory markers.

Analysis plan

The analysis plan involved three stages. First, we estimated a series of confirmatory factor analyses (CFA) to evaluate evidence of, and the interplay among, specific factors representing biological systems and a general factor representing multisystem dysregulation using combined WHAS I and II data, then in Health ABC. Second, we evaluated convergent criterion validity against clinical frailty, and predictive criterion validity with incidence of walking difficulty and mortality. Third, we tested for measurement invariance of the factor solution by age, race, and study membership (WHAS I, WHAS II, Health ABC).

Confirmatory factor analyses.—The relationship between physiological systems and multisystemic dysregulation described earlier in the conceptual framework is unclear. We compared three theoretically distinct confirmatory factor analysis models. These models test different hypotheses about the relationship between multisystemic dysregulation and dysregulation in individual systems (36). In a unidimensional model (Figure 1, panel A), multisystem dysregulation is presumed to lead directly to dysregulation in individual biomarkers; there is no representation of individual physiological systems. As this model cannot fit better than alternatives, we considered at least comparable fit of it compared to other models as evidence of no need to account for dysregulation in individual physiological systems after accounting for multisystemic dysregulation.

In a second-order CFA model (Figure 1, panel B), individual physiological systems are responsible for correlations among biomarkers within that system, and in turn, intercorrelations among individual physiological systems are explained by multisystemic dysregulation. The specific factors representing physiological systems mediate the relationship between multisystemic dysregulation and individual biomarkers. Considerably better fit of the second-order model relative to other models would be consistent with the hypothesis that multisystemic dysregulation is manifested through dysregulation in individual systems.

In a bifactor CFA model (Figure 1, panel C), each biomarker is influenced directly both by a general multisystemic dysregulation factor and a system-specific physiological factor. This model acknowledges that common covariation among all biomarkers represents underlying multisystemic dysregulation, and also that system-specific factors influence specific biomarkers beyond the influence of multisystemic dysregulation. Bifactor models have been used in prior to model multidimensionality in physiology (36) and psychopathology (48). The general and system-specific factors are independent of each other to empirically identify

the model. Considerably better fit of the bifactor model would suggest both multisystemic and systemic-specific dysregulation each have distinct, independent effects on physiology. The second-order model is nested within the bifactor model (37), facilitating direct comparison via a likelihood ratio test.

We estimated, using the expected a posteriori method (38), continuously distributed factor scores from the best-fitting model. We evaluated model fit using the root mean square error of approximation (RMSEA), Comparative Fit Index (CFI), and Tucker-Lewis Index (TLI). The RMSEA is an absolute fit index of model fit that takes into account the complexity, via degrees of freedom, of a model; values ≤0.05 indicate excellent fit. The CFI and TLI capture incremental fit relative to a null model in which all variables are uncorrelated; values of at least 0.95 are considered excellent (39).

Criterion validity.—To describe the concurrent criterion validity of multisystem dysregulation with respect to physical frailty, we estimated a logistic regression of physical frailty status on the factor score for multisystem dysregulation in WHAS data, adjusting for age and race.

To assess predictive criterion validity for future disability and for mortality, in both WHAS and Health ABC we modeled time to onset of major mobility difficulty or death using Cox proportional hazards models with the Efron method for handling ties (40). Separately for WHAS I and II, we estimated three models for each outcome. All models adjusted for age and race. First, we tested the association of the physiological factor with the time to event outcome. Second, we tested the association of physical frailty. Third, we entered the physiological factor and physical frailty into the same model. Because the physical frailty phenotype could not be precisely reproduced in Health ABC, we estimated just the first model. We evaluated the proportional hazards assumption in each dataset by visually inspecting Kaplan-Meier curves and also by testing for non-zero slopes in the regression of Schoenfeld residuals on time.

Evaluation of measurement invariance.—Biomarkers from different studies may be nonequivalent due to differences in assay techniques or storage methods. Biomarkers might also have different inter-relationships in different demographically defined groups. Thus, we estimated multiple-group versions of the best-fitting CFA model to evaluate whether patterns of dysregulation vary over age (grouped into 70–73 years, 74–79 years), race (white, non-white), or study membership (WHAS, Health ABC).

We tested three levels of invariance: configural, metric, and scalar (39). Configural invariance is met when the same biomarkers are related to the same physiological factors across groups. Metric invariance tests whether the magnitude of correlations, or factor loadings, of biomarkers with the general multisystemic and system-specific factors are equal across groups. Satisfaction of metric invariance implies the biomarkers have comparable levels of random error across groups, or more precisely that relationships with their underlying physiological systems and with multisystem dysregulation are similar across groups. Scalar invariance tests whether the severity of impairment in biomarkers, where severity is defined relative to other biomarkers, is the same across groups. Satisfaction of

scalar invariance implies metric invariance and further that biomarker thresholds for impairment are comparable across groups (e.g., that there are no systematic measurement differences).

Sensitivity analyses.—We conducted five sets of sensitivity analyses. First, we conducted criterion validity testing using scores representing general factors from the alternative models that did not fit the data as well (see Figure 1). Second, to test that the factors do not depend on any single biomarker, e.g., that multisystem dysregulation can be represented in a measurement model regardless of specific biomarkers used, we re-estimated factor analyses in WHAS after leaving out individual biomarkers one at a time. Third, to evaluate whether results are driven by individuals who are diabetic, we re-estimated factor analyses in WHAS after excluding people with diabetes (and the HbA1c indicator). Fourth, to explore whether results are similar in men, we estimated factor analyses in Health ABC among men aged 70–79 years (N=1,425) (cutpoints used for men are provided in Supplemental Table 1). Fifth, to verify that the measured scores were comparable between WHAS and Health ABC studies, we used factor loadings and thresholds from WHAS to estimate CFAs in Health ABC and evaluated criterion validity using those scores.

CFA models were estimated with Mplus software version 8 using maximum likelihood estimation. Descriptive analyses and all other modeling were conducted using Stata version 13.1. For all analyses that combined WHAS I and II data, we used inverse probability weights to weight the sample to be representative of community-living older women in the sampling frame (41). We scaled factor scores from CFA models to a half standard deviation so that when examining criterion validity, we could compare coefficients for a continuously distributed factor score with the binary frailty status (46).

Results

WHAS and Health ABC samples of older women aged 70–79 years were predominantly white (77% in WHAS, 54% in Health ABC) and most (73% in WHAS, 77% in Health ABC) had at least a high school education.

Confirmatory factor analyses.

Results of factor analyses are shown in Table 1 for WHAS and Table 2 for Health ABC. Standardized loadings in Tables 1 and 2 have a range between −1 and 1 and are interpretable as correlations between biomarkers and the factors denoted in column headers. Because factors are orthogonal to others in the same model, squared values of loadings describe the proportion of variability in a biomarker explained by the given factor in the model.

Unidimensional CFA models of physiological dysregulation demonstrated moderate to poor absolute fit to the data in WHAS (RMSEA: 0.061; CFI: 0.678; TLI: 0.607) and Health ABC (RMSEA: 0.075; CFI: 0.451; TLI: 0.329). Using WHAS data and likelihood ratio tests, the model had considerably worse fit relative to both the second-order (χ^2=84, df=2, p<0.001) and bifactor models (χ^2=137, df=15, p<0.001). The same was true of the unidimensional CFA in Health ABC (fit relative to the second-order model: χ^2=207, df=2, p<0.001; fit relative to the bifactor model: χ^2=338, df=12, p<0.001).

Although second-order models fit better than unidimensional solutions in each study, bifactor solutions provided notably the best fit in both WHAS (RMSEA: 0.019; CFI: 0.977; TLI: 0.961) and Health ABC (RMSEA: 0.047; CFI: 0.874; TLI: 0.787). The bifactor solution fit substantially better than a second-order model in WHAS (χ^2=52, df=12, p<0.001) and in Health ABC (χ^2=131, df=12, p<0.001). Considering the bifactor solution in Tables 1 and 2, standardized factor loadings on the general factor represent the correlation between a biomarker and the latent variable representing multisystem dysregulation; most loadings in WHAS were of a reasonable absolute magnitude (between 0.14 and 0.66) (42). These results are consistent with the hypothesis that both a common multisystemic physiological dysregulation factor and system-specific factors contribute independently to variation in individual biomarkers that represent dysregulation. The proportion of the variability for each biomarker explained by the model, as evidenced by squares of the standardized loadings, also tended to be greater in the bifactor model compared with the unidimensional or second-order models. For example, in the WHAS bifactor solution, squared values of coefficients show that between 0 % and 94% of variability in individual biomarkers are explained by system-specific factors, and between 0.3% and 43% of variability in markers are explained by the general factor. For most biomarkers in both studies, loadings on the general factor tend to be smaller in absolute magnitude than loadings on the system-specific factors, underscoring the substantial roll of system-specific factors among biomarkers. Some loadings on the general factor, such as for HDL cholesterol, were even negative but not statistically significantly so.

Criterion validity.

Using WHAS I and II data, a half-standard deviation elevated level of the general factor from the bifactor solution representing multisystem dysregulation was associated with a 2.2-fold increased odds of frailty (95% confidence interval, CI: 1.4, 3.5).

Table 3 presents hazard ratios (HR) for the association of the physiological factor and physical frailty with time to onset of incident mobility difficulty. Adjusting for age and race, greater levels of continuous the physiological dysregulation factor were associated with onset of mobility difficulty in WHAS I (HR=2.16, 95% confidence interval, CI: 1.42, 3.27), WHAS II (HR=1.33, 95% CI: 1.01, 1.76), and Health ABC (HR=1.59, 95% CI: 1.40, 1.80). Except for energy metabolism in Health ABC, secondary factor scores from the bifactor solution were also statistically significantly associated with onset of mobility difficulty, albeit less strongly than the general factor representing physiological dysregulation. As expected, physical frailty also was associated with time to onset of mobility difficulty (Table 3, model 2), independently of the physiological factor (Table 3, model 3).

Table 4 presents analyses of time to death. Elevated levels of the physiological dysregulation factor was associated with time to death in WHAS I (HR=1.82, 95% CI: 1.13, 2.95), WHAS II (HR=1.57, 95% CI: 1.16, 2.14), and Health ABC (HR=1.45, 95% CI: 1.24, 1.71), even after adjustment for physical frailty status.

Evaluation of measurement invariance.

To evaluate whether relationships between biomarkers and the specific and general factors in the bifactor model are comparable across data source, age, and race, we tested for measurement invariance using multiple-group bifactor models according to dataset, age groupings, and race. Parameter estimates for invariance testing by data source, age, and race are shown in Supplementary Tables 2, 3, and 4, respectively.

Across datasets, absolute fit was excellent for models conforming to configural (RMSEA=0.037; CFI=0.932), metric (RMSEA=0.040; CFI=0.900), and scalar invariance (RMSEA=0.049; CFI=0.841). These absolute fit statistics reflect utility of the bifactor model for characterizing correlations in the data. Relative fit statistics, which reflect differences in the relative distributions of biomarkers by dataset, were progressively worse for increasingly stringent levels of invariance (metric compared to configural invariance: χ^2=81, df=22, p<0.001; scalar compared to metric invariance: χ^2=115, df=9, p<0.001). The relatively worse fit of the metric model was mostly attributable to non-invariant loadings among the specific factors rather than the general factor for multisystem dysregulation; when those were allowed to vary across dataset while the loadings on the general factor were fixed across dataset, relative fit was not different from a configural model (χ^2=29, df=20, p=0.14), suggesting metric invariance was satisfied for the multisystemic dysregulation factor.

Tests of measurement invariance with respect to age and race suggested the bifactor solution was invariant by age and race. Across age, absolute fit was excellent for configural (RMSEA=0.036; CFI=0.936), metric (RMSEA=0.031; CFI=0.942), and scalar (RMSEA=0.030; CFI=0.939) invariance. Further, relative fit tests comparing configural to metric (χ^2=12, df=22, p=0.96) and metric to scalar (χ^2=13, df=9, p=0.20) invariance were statistically non-significant, implying the distributions and correlation structure of biomarkers are comparable across age. Likewise, tests of measurement invariance with respect to race demonstrated that models for configural (RMSEA=0.040; CFI=0.911), metric (RMSEA=0.034; CFI=0.918; fit relative to a configural model: χ^2=11, df=22, p=0.98), and scalar (RMSEA=0.042; CFI=0.868; fit relative to a metric model: χ^2=10, df=9, p=0.47) invariance each provided excellent absolute fit to data and that relative fit was not different by race.

Sensitivity analyses.

Relationships of general factor scores from unidimensional and second-order CFAs with mobility difficulty (Supplemental Table 5) and mortality (Supplemental Table 6) were comparable to those from the bifactor model. Neither results from factor analysis themselves, nor inferences from criterion validity, were affected when individual biomarkers were excluded from models (Supplemental Table 7). Similarly, results remained similar after excluding N=101 participants with diabetes (Supplemental Table 8). When we estimated factor analyses in men in Health ABC, the pattern of results was similar: a bifactor solution fit best (RMSEA=0.038; CFI=0.938; TLI=0.898) (Supplemental Table 9). Notably, in the bifactor solution among men in contrast to the solution for women, IL6 and CRP were more strongly correlated with the inflammatory subfactor than the general factor, while

testosterone had a greater role in the general factor. Findings with respect to criterion validity in Health ABC did not change appreciably when we estimated factor scores using item parameters from WHAS (Supplemental Table 10).

Discussion

Frailty is thought to be an emergent property that is due to dysregulation of multiple physiological systems governing homeostasis. However, it is challenging to characterize this multisystemic dysregulation and its relationship with individual physiologic systems. In this study, we combined data from three well-characterized cohorts to evaluate the factor structure of biomarkers and how individual physiological systems are related to overall multisystemic dysregulation. Findings support a construct of multisystem physiological dysregulation defined by the shared variance across biomarkers from many physiological systems, after accounting for independent effects of impairment in individual systems. Findings suggest both system-specific and system-wide processes have unique and non-overlapping contributions to dysregulation in biological markers; the large loadings on system-specific factors highlight their substantial role. The multisystem dysregulation factor is associated with frailty, as well as an elevated hazards of incident mobility difficulty and death.

These findings are consistent with previous research. Previous studies using other approaches have suggested that overall multi-system physiologic dysregulation is not independent of system-specific dysregulation, yet is more than the sum of system-specific dysregulation (7). Using data from the Midlife in the United States II Biomarker Project (N=1,255), Wiley and colleagues (36) tested alternative factor structures of biomarkers to model allostatic load and found a bifactor solution fit the data considerably better than a second-order model, and further was invariant across age and sex. Although this study considered continuously distributed versions of biomarkers, some of which overlapped with the set we evaluated, to model allostatic load, we used binary versions of biomarkers to model more explicitly multisystem physiological dysregulation.

Future research at epidemiologic but also biological level is needed to better understand the nature of any substrate underlying the multisystemic physiological dysregulation that we have operationalized using latent variable modeling, and that others have also hypothesized to exist. We used one latent variable approach, based on common correlations shared by indicators of dysregulated biomarkers, to model multisystemic physiological dysregulation. Other research has approached this goal in other ways. Latent variable models, used here, have been applied to multiple biomarkers of particular systems, although there are exceptions that have evaluated biomarkers spanning several systems (12,36). An important caveat to keep in mind regarding latent variable modeling is that in interpreting from bifactor models that both system-specific and system-wide processes have unique and non-overlapping “contributions” to dysregulation - and that generalized multisystem dysregulation “causes” system-specific dysregulations in the second-order model - we are invoking a local homogeneity assumption (47). This assumption is that a measurement model has the same form within and between people; in other words, correlation based on between-persons variation in biomarkers is being modeled to make inferences about within-

person causal processes. This is an inherent limitation for any statistical attempt to quantify causal relationships among bodily processes using between-persons variation, thus careful interpretations should be accompanied by appropriate skepticism. Other studies have modeled multisystem dysregulation using cross-sectional sum scores (e.g., 43–44) or Mahalanobis distance (7,10–11). Belsky and colleagues (45) quantified biological “pace of aging” based on longitudinal trajectories of 18 biomarkers among middle-aged adults in their 30s and 40s. Unlike other studies, including ours, this study was able to distinguish within-person change from between-persons change. Ultimately, evidence for a substrate underlying multisystemic physiological dysregulation must come from multiple types of models and information.

The role of multisystem dysregulation in physical frailty remains an open question. Part of our ultimate goal is to hypothesize and validate an endophenotype for frailty. It remains a hypothesis that clinical manifestation of physical frailty results from loss of complex interactions among interrelated physiological networks. According to this theory, multisystem dysregulation leads to elevated vulnerability to stressors and a decreased ability to recover normal homeostasis (12). While rates of deterioration may vary across systems and between groups of people, nearly all physiological systems are probably affected by frailty to some degree. We do not claim that the current model is exhaustive: we are limited by the current state of knowledge and the availability of consistently measured biomarkers across the studies used. Indeed, the physiologic factor in our study was associated with adverse outcomes independently of clinical frailty. This finding suggests either that the physiological basis of frailty we have derived includes factors external to frailty (and even that consideration of other systems and other biomarkers is merited), or that the frailty phenotype measure is an imperfect measure of frailty. Either hypothesis is reasonable and both merit further investigation and measurement refinement.

The findings in our study may be a snapshot of a progressive process of multisystemic deterioration in frailty. It may be that individuals presenting with multiple system physiological dysregulation may be more downstream in the frailty process, and their first dysregulated system occurred several years prior to observation. Pursuant to this reasoning, a population of relatively healthy people should not show evidence of multisystemic dysregulation via a bifactor solution of biomarkers from diverse body systems. To provide direct support for this hypothesis, more extensive data are needed on the longitudinal co-evolution of multiple biomarkers over a long time span prior to development of frailty. We report in this study a cross-sectional correlation between multisystem dysregulation and clinical frailty that, while strong, is not causal.

There are several caveats and future directions for this study. First, tests of measurement invariance implied that the global cutoffs (either at one or both extremes of a biomarker distribution) we used for each biomarker may be sufficient to indicate dysregulation across different groups. Future investigations are necessary to evaluate invariance over wider age ranges, as well as with respect to sex. Second, we did not consider an exhaustive list of biomarkers from all possible physiological systems. Several other physiological systems may be altered in multisystem dysregulation, including the autonomic nervous system, sympathetic nervous system, and renin angiotensin system (7,36). Because the datasets used

in the present study do not have adequate - or comparable - markers of these systems, we were unable to include biomarkers of these systems. Other studies have considered different biomarkers using varying modeling approaches and have generally concluded that multisystemic physiological dysregulation exists separately from dysregulation in individual systems (7,11,36). Our findings, while not inclusive of all potential biomarkers from all physiological systems, are consistent with these findings and further suggest that system-specific and general physiological dysregulation should be modeled in tandem to adequately represent observed impairment in biomarkers. A final caveat of this study is that measurement error in biomarkers is likely pervasive. Such measurement error may arise from natural variation (e.g., diurnal changes), assay differences, medications, etc. While such errors likely weaken intercorrelations among biomarkers, thereby weakening the strength of the general multisystemic dysregulation factor, our factor analysis approach is more optimal than incorporating biomarkers into a composite scale (e.g., summation or averaging) because the multisystemic dysregulation factor represents the common covariation among the biomarkers.

An important future direction that requires not only empirical data analysis but also input from substantive theory is what other physiological systems and what other biological markers may be salient markers of multisystem dysregulation. We speculate that the autonomic nervous system, sympathetic nervous system, and renin angiotensin system may be viable critical candidate systems, for example. Biomarkers comprising individual systems also needs attention; testosterone was a poor marker of multisystemic dysregulation in Health ABC among women but not men, while the markers we selected for energy metabolism were more strongly correlated with the specific factor than with the general multisystemic factor.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Multifactorial biological processes underpin dysregulation over multiple physiological systems. How best to juxtapose the former in relation to individual dysregulated systems remains understudied.
- We operationalized a theory-driven measure of multisystem dysregulation by fitting several alternative theory-driven measurement models of biomarkers representing multiple physiological systems. Based on theory, previous research, and data availability, we chose to represent physiological systems related to stress response (e.g., inflammation), those related to interconnections among endocrine systems, and energy and nutrient metabolism.
- Findings support a construct of multisystem physiological dysregulation as the shared variance across biomarkers from many physiological systems, after accounting for independent effects of impairment in individual physiological systems. Individual systems still account for unique variation in the biomarkers, suggesting both system-specific and system-wide processes have unique and non-overlapping contributions to dysregulation in biological markers.
- The multisystem dysregulation factor is associated with frailty, as well as an elevated hazards of incident mobility difficulty and death.

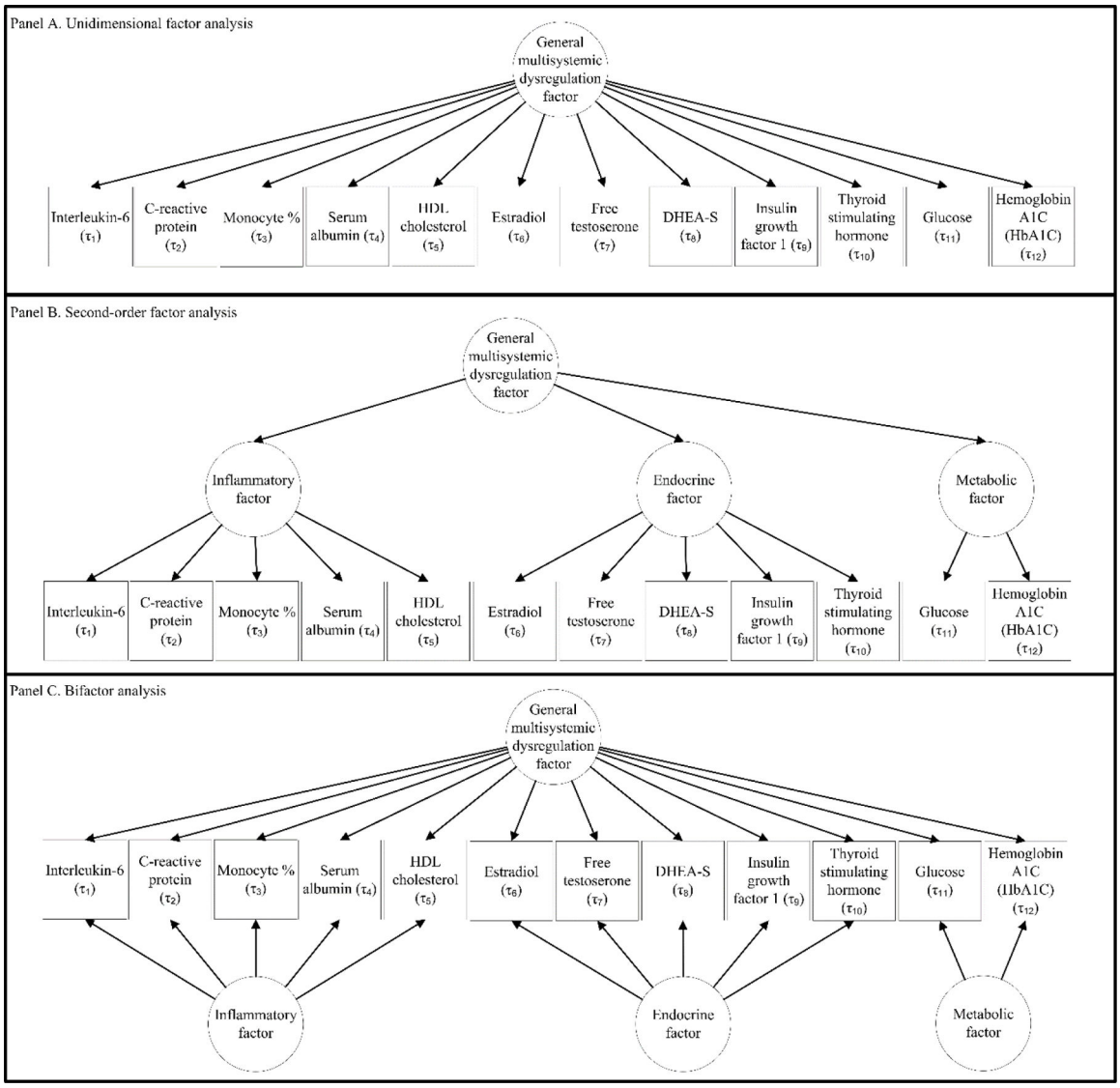

Figure 1. Path diagrams for alternative hypotheses regarding system-wide and system-specific multisystem dysregulation, and their relationship

Legend. This figure depicts three alternative confirmatory factor analysis (CFA) models tested in this study to represent multisystem dysregulation; see text for substantive interpretations. Observed indicators for dysregulated biomarkers are displayed in squares. Latent variables for general and systemic-specific latent variables, which represent common covariation in observed indicators to which arrows point, are shown in circles.

Table 1.

Factor analysis results in WHAS I and II (N=649)

Variabl e	**Single-factor**		**Second-order model**					**Bifactor model**			
	Standardized loading		**Standardized loading, General factor**	**Standardized loading, Inflammation**	**Standardized loading, Endocrine**	**Standardized loading, Energy metabolism**		**Standardized loading, General factor**	**Standardized loading, Inflammation**	**Standardized loading, Endocrine**	**St lo E m**
Interleukin-6 (IL6)	0.39			0.54				0.20	0.48		
C-reactive protein (CRP)	0.47			0.59				0.38	0.47		
Monocyte %	0.18			0.21				0.18	0.16		
Serum albumin	0.68			0.78				0.66	0.56		
HDL cholesterol	0.39			0.49				−0.18	0.71		
Estradiol	−0.20				0.43			−0.29		0.46	
Free testoserone	−0.17				0.64			0.14		0.66	
DHEA-S	−0.16				0.72			0.06		0.68	
Insulin growth factor 1 (IGF1)	0.18				0.16			0.62		0.21	
Thyroid stimulating hormone (TSH)	0.20				−0.07			0.36		−0.08	
Glucose	0.73					0.91		0.16			0.
Hemoglobin	0.96					0.91		0.31			0.
A1C (HbA1 C)											
Inflammatory factor			0.74								
Endocrine factor			−0.17								
Metabolic factor			0.69								
Model fit											
RMSEA	0.061		0.038					0.019			
CFI	0.678		0.881					0.977			
TLI	0.607		0.849					0.961			
chi2	188.258				133.626			45.833			
df	24				26			39			
p-value					0			0			
	54.632							87.793			

Variabl e	**Single-factor**		**Second-order model**					**Bifactor model**			
	Standardized loading		**Standardized loading, General factor**	**Standardized loading, Inflammation**	**Standardized loading, Endocrine**	**Standardized loading, Energy metabolism**		**Standardized loading, General factor**	**Standardized loading, Inflammation**	**Standardized loading, Endocrine**	**St lo E m**
	142.425										
Variable	**Single-factor**		**Second-order model**					**Bifactor model**			
	Standardized loading		**Standardized loading, General factor**	**Standardized loading, Inflammation**	**Standardized loading, Endocrine**	**Standardized loading, Energy metabolism**		**Standardized loading, General factor**	**Standardized loading, Inflammation**	**Standardized loading, Endocrine**	**St lo E m**
Interleukin-6 (IL6)	0.25			0.73				0.08	0.45		
C-reactive protein (CRP)	0.19			0.58				0.77	0.87		
Monocyte %	−0.09			−0.03				0.17	−0.05		
Serum albumin	0.00			0.16				0.04	0.09		
HDL cholesterol	0.23			0.25				−0.23	0.24		
Estradiol	0.04				0.92			−0.46		0.96	
Free testoserone	0.02				0.11			0.08		0.06	
DHEA-S	−0.09				0.34			−0.04		0.31	
Insulin growth factor 1 (IGF1)	−0.04				0.30			0.17		0.35	
Thyroid stimulating hormone (TSH)	−0.12				0.04			0.16		0.10	
Glucose	0.68					0.81		−0.51			0.
Hemoglobin A1C (HbA1C)	0.55					0.95		−0.52			0.
Inflammatory factor			0.707								
Endocrine factor			−0.076								
Metabolic Factor			0.591								
Model fit											
RMSEA	0.075		0.057					0.047			
CFI	0.451		0.761					0.874			
TLI	0.329		0.691					0.787			
					267.163			137.78			

Variabl e	**Single-factor**		**Second-order model**					**Bifactor model**			
	Standardized loading		**Standardized loading, General factor**	**Standardized loading, Inflammation**	**Standardized loading, Endocrine**	**Standardized loading, Energy metabolism**		**Standardized loading, General factor**	**Standardized loading, Inflammation**	**Standardized loading, Endocrine**	**St lo E m**
chi2	558.384				291.221			153.441			
df	36				26			38			
p-value					6.39E-137			1.02E-47			

Table 2.

Factor analysis results in Health ABC (N=1515)

Variable	Single-factor	Second-order model				Bifactor model			
	Standardized loading	Standardized loading, General factor	Standardized loading, Inflammation	Standardized loading, Endocrine	Standardized loading, Energy Metabolism	Standardized loading, General factor	Standardized loading, Inflammation	Standardized loading, Endocrine	Standardized loading, Energy metabolism
Interleukin-6 (IL6)	0.39		0.54			0.20	0.48		
C-reactive protein (CRP)	0.47		0.59			0.38	0.47		
Monocyte %	0.18		0.21			0.18	0.16		
Serum albumin	0.68		0.78			0.66	0.56		
HDL cholesterol	0.39		0.49			−0.18	0.71		
Estradiol	−0.20			0.43		−0.29		0.46	
Free testoserone	−0.17			0.64		0.14		0.66	
DHEA-S	−0.16			0.72		0.06		0.68	
Insulin growth factor 1 (IGF1)	0.18			0.16		0.62		0.21	
Thyroid stimulating hormone (TSH)	0.20			−0.07		0.36		−0.08	
Glucose	0.73				0.91	0.16			0.78
Hemoglobin A1C (HbA1C)	0.96				0.91	0.31			0.97
Inflammatory factor		0.74							
Endocrine factor		−0.17							
Metabolic factor Model fit		0.69							
RMSEA	0.061	0.038				0.019			
CFI	0.678	0.881				0.977			
TLI	0.607	0.849				0.961			
chi2	188.258			133.626		45.833			
df	24			26		39			
p-value				0		0			
	54.632					87.793			
	142.425								
Variable	Single-factor	Second-order model				Bifactor model			

Variable	Single-factor	Second-order model				Bifactor model			
	Standardized loading	**Standardized loading, General factor**	**Standardized loading, Inflammation**	**Standardized loading, Endocrine**	**Standardized loading, Energy Metabolism**	**Standardized loading, General factor**	**Standardized loading, Inflammation**	**Standardized loading, Endocrine**	**Standardized loading, Energy metabolism**
	Standardized loading	Standardized loading, General factor	Standardized loading, Inflammation	Standardized loading, Endocrine	Standardized loading, Energy Metabolism	Standardized loading, General factor	Standardized loading, Inflammation	Standardized loading, Endocrine	Standardized loading, Energy metabolism
Interleukin-6 (IL6)	0.25		0.73			0.08	0.45		
C-reactive protein (CRP)	0.19		0.58			0.77	0.87		
Monocyte %	−0.09		−0.03			0.17	−0.05		
Serum albumin	0.00		0.16			0.04	0.09		
HDL cholesterol	0.23		0.25			−0.23	0.24		
Estradiol	0.04			0.92		−0.46		0.96	
Free testoserone	0.02			0.11		0.08		0.06	
DHEA-S	−0.09			0.34		−0.04		0.31	
Insulin growth factor 1 (IGF1)	−0.04			0.30		0.17		0.35	
Thyroid stimulating hormone (TSH)	−0.12			0.04		0.16		0.10	
Glucose	0.68				0.81	−0.51			0.67
Hemoglobin A1C (HbA1C)	0.55				0.95	−0.52			0.73
Inflammatory factor		0.707							
Endocrine factor		−0.076							
Metabolic factor		0.591							
Model fit									
RMSEA	0.075	0.057				0.047			
CFI	0.451	0.761				0.874			
TLI	0.329	0.691				0.787			
				267.163		137.78			
chi2	558.384			291.221		153.441			
df	36			26		38			
p-value				6.39E-137		102E-47			

Table 3.

Predictive criterion validity: Results from survival analyses for mobility difficulty in WHAS and Health ABC

	WHAS I		WHAS II		Health ABC	
Sample size	263		380		1499	
Incident mobility difficulty	73		202		992	
Person-years at risk	680.8		3009.6		10313.7	
Model 1. Physiologic factor, HR (95% CI)	2.16	1.42, 3.27	1.33	1.01, 1.76	1.59	1.40, 1.80
Model 2. Frailty, HR (95% CI)	2.80	1.69, 4.63	2.09	0.97, 4.48		
Model 3. Physiologic factor, HR (95% CI)	2.23	1.45, 3.43	1.35	1.02, 1.79		
Model 3. Frailty, HR (95% CI)	2.54	1.54, 4.19	2.21	1.03, 4.76		
Model 4. Physiologic factor, HR (95% CI)	1.85	1.04, 3.31				
Model 4. Frailty, HR (95% CI)	2.28	1.26, 4.14				
Model 4. Interaction of frailty and physiologic factor, HR (95% CI)	0.95	0.41, 2.19				

	WHAS I		WHAS II		Health ABC	
Sample size	262		384		1499	
Deaths	53		156		567	
Person-years at risk	1159.6		3710.7		16283.7	
Model 1. Physiologic factor, HR (95% CI)	1.82	1.13, 2.95	1.57	1.16, 2.14	1.45	1.24, 1.71
Model 2. Frailty, HR (95% CI)	1.74	0.95, 3.20	2.16	0.95, 4.91		
Model 3. Physiologic factor, HR (95% CI)	1.88	1.15, 3.09	1.61	1.18, 2.18		
Model 3. Frailty, HR (95% CI)	1.60	0.87, 2.93	2.35	1.03, 5.35		
Model 4. Physiologic factor, HR (95% CI)	1.66	0.85, 3.24				
Model 4. Frailty, HR (95% CI)	0.88	0.40, 1.92				
Model 4. Interaction of frailty and physiologic factor, HR (95% CI)	0.36	0.13, 1.01				

Legend. All models are adjusted for age and race. Coefficients for the physiologic factor are interpretable as the hazard ratio for mobility difficulty per half standard deviation increase in the physiologic factor. Coefficients for frailty are interpretable as a hazard ratio between frail and nonfrail participants.

Table 4.

Predictive criterion validity: Results from survival analyses for mortality in WHAS and Health ABC

	WHAS I		WHAS II		Health ABC	
Sample size	263		380		1499	
Incident mobility difficulty	73		202		992	
Person-years at risk	680.8		3009.6		10313.7	
Model 1. Physiologic factor, HR (95% CI)	2.16	1.42, 3.27	1.33	1.01, 1.76	1.59	1.40, 1.80
Model 2. Frailty, HR (95% CI)	2.80	1.69, 4.63	2.09	0.97, 4.48		
Model 3. Physiologic factor, HR (95% CI)	2.23	1.45, 3.43	1.35	1.02, 1.79		
Model 3. Frailty, HR (95% CI)	2.54	1.54, 4.19	2.21	1.03, 4.76		
Model 4. Physiologic factor, HR (95% CI)	1.85	1.04, 3.31				
Model 4. Frailty, HR (95% CI)	2.28	1.26, 4.14				
Model 4. Interaction of frailty and physiologic factor, HR (95% CI)	0.95	0.41, 2.19				

	WHAS I		WHAS II		Health ABC	
Sample size	262		384		1499	
Deaths	53		156		567	
Person-years at risk	1159.6		3710.7		16283.7	
Model 1. Physiologic factor, HR (95% CI)	1.82	1.13, 2.95	1.57	1.16, 2.14	1.45	1.24, 1.71
Model 2. Frailty, HR (95% CI)	1.74	0.95, 3.20	2.16	0.95, 4.91		
Model 3. Physiologic factor, HR (95% CI)	1.88	1.15, 3.09	1.61	1.18, 2.18		
Model 3. Frailty, HR (95% CI)	1.60	0.87, 2.93	2.35	1.03, 5.35		
Model 4. Physiologic factor, HR (95% CI)	1.66	0.85, 3.24				
Model 4. Frailty, HR (95% CI)	0.88	0.40, 1.92				
Model 4. Interaction of frailty and physiologic factor, HR (95% CI)	0.36	0.13, 1.01				

Legend. All models are adjusted for age and race. Coefficients for the physiologic factor are interpretable as the hazard ratio for mortality per half standard deviation increase in the physiologic factor. Coefficients for frailty are interpretable as a hazard ratio between frail and nonfrail participants.