Mechanisms of Ageing and Development 183 (2019) 111130

Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev

Feed-forward loop between body composition, strength and performance in older adults

Arindam RoyChoudhury[a,*,1], Thuy-Tien L. Dam[b,1], Chenghuiyun Xu[a], Jonathan H. Diah[b], Deepa Chaganty[c], Jonathan Solares[d], Linda P. Fried[e]

[a] Division of Biostatistics and Epidemiology, Department of Healthcare Policy and Research, Weill Cornell Medicine, Cornell University, New York, NY, United States
[b] Department of Medicine, Vagelos College of Physicians and Surgeons, Columbia University Medical Center, Columbia University, New York, NY, United States
[c] Department of Statistics, University of Virginia, Charlottesville, VA, United States
[d] Department of Biostatistics, University of North Carolina, Chapel Hill, NC, United States
[e] Mailman School of Public Health, Columbia University Medical Center, Columbia University, New York NY, United States

ARTICLE INFO

Keywords:
Frailty
Sarcopenia
Body composition
Physical activity
Grip strength

ABSTRACT

Frailty syndrome is hypothesized to arise from malfunction in feedback mechanisms among interacting physiological systems. However, empirical evidence to support this hypothesis is not yet available. We present evidence of a feed-forward loop relationship between certain components of the frailty syndrome: body composition, strength and physical performance level.

The evidence has been found by performing statistical analysis on measures from 878 females and 588 males aged 60–97, participating in the Rancho Bernardo Study, followed for at least three visits over 12 years. In the analysis, we have used fat mass and lean mass (measured by whole body DXA scans), grip strength (measured by dynamometer) and time to get up and walk a certain distance. The results provide evidence of a feed-forward loop between these variables. The results also suggest that adverse changes in body composition would not only reduce the physical performance and grip strength, but the changes would further result in adverse changes in body composition. Our findings support the hypothesis that feed-forward loops are present between the components of the frailty syndrome at the time of development of frailty, which itself may be a manifestation of dysregulated energetics.

1. Introduction

Frailty is a geriatric syndrome that identifies vulnerable older adults with an underlying distinct pathophysiology (Fried et al., 2009) who are at increased risk for poor health outcomes (Fried et al., 2001; Morley et al., 2013). This syndromic phenotype includes five symptoms: weakness, slowness, physical inactivity, unintentional weight loss, and fatigue (Fried et al., 2001). Those having at least three of the symptoms are designated as “frail”, consistent with the definition of a syndrome.

Using this definition, the prevalence of frailty among community-dwelling adults ≥ 65 in the Cardiovascular Health Study (CHS) was 6.9% (Fried et al., 2001), 11.3% among women 70–79 in the Women’s Health and Aging Studies I & II combined (WHAS) (Bandeen-Roche et al., 2006), and 8% in community-dwelling men in the Osteoporotic Fractures in Men Study (MrOS) (Cawthon et al., 2007). Frail older adults have a 2-fold higher risk of falls, fractures, hospitalizations, disability, and early death (Fried et al., 2001; Cawthon et al., 2007). Likewise, this phenotype has been useful in identifying patients who may recover poorly after surgery and require institutionalization (Makary et al., 2010).

Numerous physiologic changes are seen in phenotypically frail adults, including sarcopenia, or decreased lean body mass; increased pro-inflammatory markers, decreased immune response, elevated oxidative stress (Walston et al., 2002), multiple hormonal deficiencies (Cappola et al., 2009), altered autonomic nervous system and nutrition status (Semba et al., 2006), and insulin resistance (Barzilay et al., 2009). It is hypothesized that frailty results, in part, from loss of function in feedback mechanisms among the interacting systems regulating these physiologic changes. Dysregulation of these components of complex systems may impair the dynamic inherent in maintaining homeostasis and resilience.

* Corresponding author.
E-mail address: arr2014@med.cornell.edu (A. RoyChoudhury).
[1] Contributed Equally.

https://doi.org/10.1016/j.mad.2019.111130
Received 20 January 2019; Received in revised form 27 June 2019; Accepted 20 August 2019
Available online 29 August 2019
0047-6374/

However, empirical evidence that the phenotype of frailty is a manifestation of multisystem dysregulation is not yet available. To date, some studies have shown acute dysregulation of multiple physiologic systems in the frail subjects in response to stressors (Kalyani et al., 2012a,b; González-Fernández et al., 2014). Furthermore, most of the demonstrated biological relationships have largely been cross-sectional, focused on a single-system, using analytic models that have generally been unidirectional, simplified, and/or static. Most studies of multisystem vulnerability to stressors, to date, are constrained by limitation of data and methods used.

Two approaches to analyze multisystem dysregulation in older adults have been proposed to overcome these limitations. First, a general framework using dynamic systems modeling over short time intervals was proposed (Varadhan et al., 2008). This stimulus-response paradigm could examine the timing of recovery from a single stimulus, but would not address most dynamic systems where multiple stimuli occur repeatedly over time and on different time scales. Cohen et al. (2013) also introduced a distance-based approach for predicting and detecting multisystem impairment. This method, however, does not explicitly model multiple influences between variables and cannot be used to model feedback mechanisms or loop structures that are inherent to complex dynamical system.

In this context, a feedback mechanism is a mechanism with multiple steps from multiple changing systems. That is, a feedback mechanism between the systems is a part of dynamic systems. Thus, an evidence for feedback mechanism is also an evidence for dynamic systems. Therefore, it is important to seek evidence for feedback mechanism.

We have recently introduced a third statistical approach to examine feedback mechanisms in frailty. This method incorporates feed-forward loop (FFL) structures–a salient feature of complex systems whereby a variable influences its own future values directly or indirectly through other variable(s) (RoyChoudhury et al., 2014).

The objective of our current study was to examine whether feed-forward loops exist between measures of muscle mass, fat mass, strength, and/or speed of physical performance in frail community-dwelling older men and women. Specifically, we hypothesize that there is a positive feedback mechanism between muscle mass and strength/speed of physical performance; and between lean mass/fat ratio, strength and speed of physical performance. We examine here the hypothesis that feed-forward loops exist between components of frailty: body composition and strength, as physiologic and phenotypic components of the frailty syndrome

2. Materials and methods

2.1. Participants

The Rancho Bernardo Study (RBS) is a longitudinal observational cohort study, based in Rancho Bernardo, California. Any community dwelling adults in Rancho Bernardo Community between 1972 and 1974 were eligible for enrolment in the study. As this was primarily a retirement community, the residence had higher median age than the general population. Eighty two percent of the participants were 30 years of age or older. In 1992, surviving participants were invited to participate in a study to understand the epidemiology of osteoporosis. A subset of participants returned for reexamination at Visit 7, undergoing body composition and physical performance assessments (Castillo et al., 2003). The subjects were subsequently followed for 12 years with repeated measurements of body composition and physical performance approximately every 4 years.

For this analysis, Visit 7 is considered the baseline visit. We have studied 1466 older adults who were 60 years or older in Visit 7, and had their physical performance and physiological measures recorded in Visit 7. All participants provided written informed consent. The University of California San Diego Institutional Review Board approved the study protocol.

2.2. Body composition

At each examination whole body scan using fan-beamed dual energy x-ray absorptiometry (DXA) were used to measure fat mass and lean mass (Castillo et al., 2003). The same scanner model was used at all visits (Hologic 2000, Hologic, Inc., Bedford, MA, USA). Standardized procedures for participant positioning and scan analysis were followed for all scans. All DXA operators were centrally certified on scanning and analysis techniques. The validity and reproducibility of DXA have been reported previously (Salamone et al., 2000; Visser et al., 1999). The ratio of lean and fat mass was then computed. Appendicular lean mass (ALM) was calculated as the sum of non-bone lean mass from both arms and legs. Participants missing lean mass measurements for an arm or leg were excluded. These measurements were recorded longitudinally over at least three visits.

2.3. Grip strength and physical performance

Grip strength was measured for each hand twice using a handheld dynamometer (Sammons Preston Rolyan, Bolingbrook, IL, USA); for each subject, the maximum value from each hand was recorded. The average of the maximum grip strengths of the two hands was used for analysis (Härkönen et al., 1993). As a measure of physical performance we used a commonly-used measure of mobility and lower extremity function: the timing in Timed “Up and Go” test (TUG) (Herman et al., 2011). For the TUG, participants were instructed to rise from a chair, walk 3 m, and return to a sitting position. Two trials of the TUG were performed by each participant and each recorded to the tenth of a second; the average of time from these two trials were used for the analyses. This measure describe walking and rising speeds. Increasing time to perform these activities reflect poorer performance. Like body composition measures, this measurement was also obtained longitudinally over three or more visits.

2.4. Statistical analysis

We analyzed the whole cohort for Visits 7–10, which spanned over approximately 12 years. We employed the feed-forward loop model of RoyChoudhury et al. (2014) for two-variable loop, as well as generalizing it to three-variable loops. In particular, we explored several two- and three-variable feed-forward loop models between appendicular lean mass (ALM) (g), lean mass/fat ratio, TUG (sec) and grip strength (kg). Lean mass/fat ratio was converted to $\log_2$, so that one unit decrease (or increase) in the converted variable is equivalent to halving (or doubling) of the ratio. TUG was not recorded in Visit 7, and therefore we only used the data from Visits 8–10 to estimate the models involving TUG. Each variable was separately standardized within each visit, before the analyses were performed. After the analyses, the statistical relations between variables were converted back to the original units, for ease of interpretation.

A graphical representation of our two- and three-variable feed-forward loop models is given in Fig. 1a and b. In this representation the examples of loops between ALM, grip strength and TUG are used. However, the same underlying models were used for the other analyses as well. Separately for each analysis, we excluded any subjects with at least one missing variables that were needed for the analysis. As the missing values were missing completely at random, our results are not significantly affected by the missing values. The models were fitted by structural equation modeling (SEM) using the package “sem” of the software R v4.4.0.

3. Results

The baseline characteristics of the cohort are reported in Tables 1 and 2. Mean age of the participants was 75 ± 8 (range 60–97 years) at baseline, and 60% were female. They also had a mean weight of 154

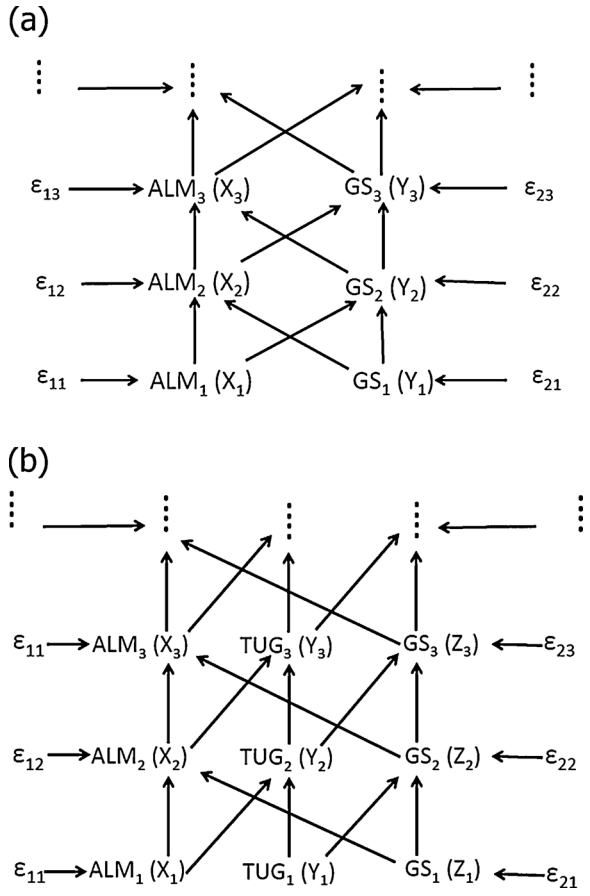

Fig. 1. (a) Feed-forward loop between appendicular lean mass or ALM(X) and grip strength or GS(Y).The Indices in ALM and GS correspond to different points in time(= 1,2,3,…). (b) Feed-forward loop between appendicular lean mass or ALM(X),timed" up and go" or TUG (Y) and grip strength or GS(Z).The Indices in ALM,TUG and GS correspond to different points in time(= 1,2,3,…).

lbs., a mean height of 66 in. and a mean BMI of 25. Among the participants, 31% reported hypertension, 24% had a history of cancer, 1% had a history of stroke, and 2% had a history of coronary bypass surgery. Their mean appendicular lean mass was 17,377 g, grip strength was 24 kg, and $\log_2$ scaled lean mass/fat mass ratio was 1.16, which is about 223%. The data on timed "up and go" were not collected on Visit 7. On Visit 8, their mean timed "up and go" time was 11.3 s.

We tested for the hypothetical feed-forward loop relationship between components of frailty: physiology (ALM) and phenotype (grip strength). We first evaluated the relationship between appendicular lean mass and grip strength. A significant two-variable FFL was detected between ALM and grip strength (Fig. 2a). After converting to original units, it is estimated that 1 g lower ALM and 1 kg lower grip strength at time 1 are associated with, respectively, 0.79 g and 65 g lower ALM at time 2 ($p < 0.001$ for both). The loop also estimated that 1 g lower ALM and 1 kg lower grip strength at time 1 are associated with, respectively, 0.27 g and 0.81 kg lower grip strength at time 2 ($p < 0.001$ for both).

Another significant two-variable FFL was detected between lean mass/fat ratio and grip strength (Fig. 2b). After converting to original units, it is estimated that 1 kg lower grip strength and 1 unit lower $\log_2$ scaled lean/fat ratio (one unit decrease in $\log_2$ scale is equivalent to halving the ratio) at time 1 are associated with, respectively, 0.03 and 0.92 unit lower $\log_2$ scaled (˜ 2% and ˜ 47% lower raw values, respectively) lean mass/fat ratio at time 2 ($p < 0.001$ for both). The loop also estimated that 1 unit lower $\log_2$ scaled lean mass/fat ratio and 1 kg lower grip strength in time 1 are associated with, respectively, 28 g and 0.92 kg lower grip strength at time 2 ($p < 0.001$ for both). These are significant findings as well and provide insight into mechanism of frailty by providing evidence that grip strength and lean mass/fat ratio affect each other as a feed-forward loop.

We examined a three-variable FFL and detected significant FFL between ALM, TUG, and grip strength (Fig. 2c). After converting to original units,1 g lower ALM and 1 g lower grip strength at time 1 are associated with, respectively, 0.79 and 0.07 g lower ALM at time 2 ($p < 0.001$ for both). The loop also estimated that 1 s increase in TUG and 1 kg lower ALM at time 1 are associated with, respectively, 0.58 and 0.11 s increase in TUG at time 2 ($p < 0.001$ for both). Finally, the loop also estimated a third equation which showed that 1 kg lower grip strength and 1 s increase in TUG at time 1 are associated with, respectively, 0.90 and 99 g lower grip strength at time 2 ($p < 0.001$ for both).

Finally, we found a significant three-variable feed-forward loop between lean/fat ratio, TUG, and grip strength (Fig. 2d). After converting to original units, it is estimated that 1 unit lower $\log_2$ scaled lean mass/fat ratio (one unit decrease in $\log_2$ scale is equivalent to

Table 2
Baseline Age Distribution in 1992 (1466 Subjects).

Age		60–69	70–79	80–89	90–99
% (n)	Overall	28.04 (411)	39.50 (579)	29.33 (430)	3.14 (46)
	Male	32.31 (190)	38.10 (224)	27.38 (161)	2.21 (13)
	Female	25.17 (221)	40.43 (355)	30.64 (269)	3.76 (33)

Table 1
Baseline Characteristic in 1992 (1466 Subjects[a]).

Characteristics	Mean ± SD (range) or % (n)		
	Overall	Male	Female
Age (year)	75 ± 8 (60, 97)	74 ± 9 (60, 95)	75 ± 8 (60, 97)
Weight (lb)	154 ± 30 (85, 278)	177 ± 25 (127, 278)	138 ± 22 (85, 230)
Height (in)	66 ± 3.7 (53, 77)	69 ± 2.5 (61, 77)	63 ± 2.3 (53, 71)
BMI (kg/m^2)	25 ± 3.9 (16, 45)	26 ± 3.6 (17, 43)	25 ± 4.0 (16, 45)
Gender % (n)	F: 60 (878); M: 40 (588)	–	–
Diabetes % (n)	Y: 96 (946); N: 4 (41)	Y: 95 (381); N: 5 (21)	Y: 97 (565); N: 3 (20)
Hypertension % (n)	Y: 31 (329); N: 69 (725)	Y: 31 (136); N: 69 (300)	Y: 31 (193); N: 69 (425)
History of cancer % (n)	Y: 24 (252); N: 76 (797)	Y: 24 (106); N: 76 (328)	Y: 24 (146); N: 77 (469)
History of stroke % (n)	Y: 1 (13); N: 99 (1027)	Y: 2 (8); N: 98 (423)	Y: 1 (5); N: 99 (604)
History of coronary bypass surgery % (n)	Y: 2 (18); N: 98 (1036)	Y: 3 (12); N: 97 (424)	Y: 1 (6); N: 99 (612)
Appendicular Lean Mass (g)	17,377 ± 4,734 (8,280 39,872)	22,111 ± 3,379 (13,531, 39,872)	14,168 ± 2,090 (8,280, 23,389)
Log_2(lean mass/fat mass)	1.16 ± 0.57 (-0.66, 2.90)	1.61 ± 0.39 (0.09, 2.90)	0.86 ± 0.46 (-0.66, 2.42)
Grip strength (maximal, kg)	24 ± 10 (3, 60)	34 ± 8 (9, 60)	18 ± 5 (3, 32)

[a] The data for each characteristic has missing observations.

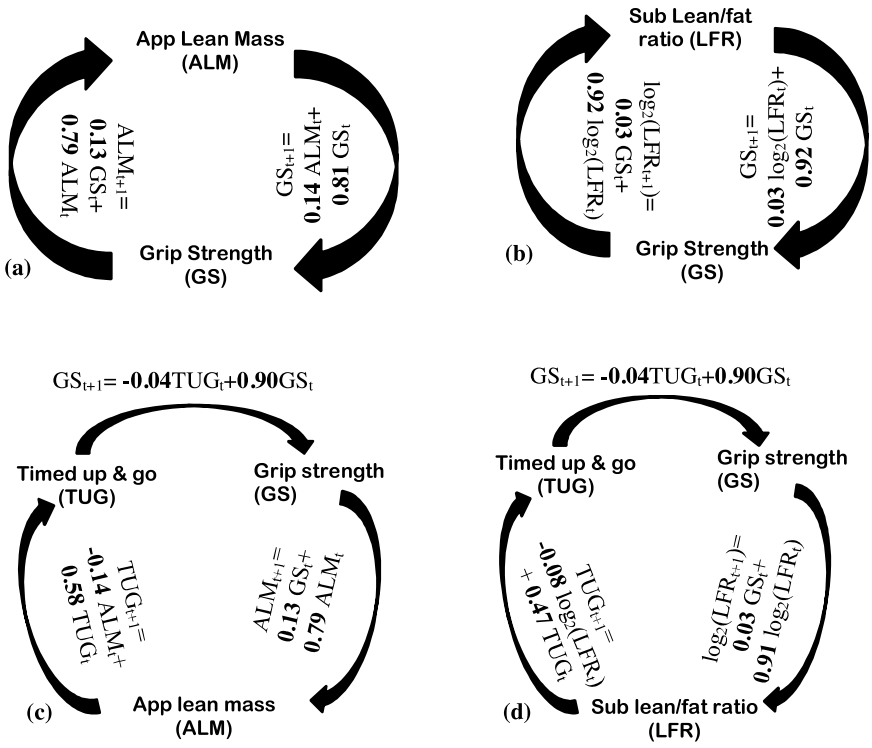

Fig. 2. a–d displays the study findings supporting feed-forward loops on our examinations of two of the five core criteria of frailty (weakness and slowness) and the underlying physiologic and functional measures. Results from each predictive feed-forward loop analysis are displayed. a: feed-forward loop between ALM and GS; b: feed-forward loop between LFR and GS; c: feed-forward loop between TUG, GS and ALM; d: feed-forward loop between TUG, GS and LFR.

halving the ratio), and 1 kg lower grip strength at time 1 are associated with, respectively, 0.91 and 0.03 unit lower $\log_2$ scaled (˜ 47% and ˜2% lower raw value, respectively) lean mass/fat ratio at time 2 ($p < 0.001$ for both). It is also estimated that 1 s increase in TUG and 1 unit lower $\log_2$ scaled lean mass/fat ratio at time 1 are associated with, respectively, 0.47 and 0.03 s increase in TUG at time 2 ($p < 0.001$ for both). Finally, the loop also estimated that 1 kg lower grip strength and 1 s increase in TUG at time 1 are associated with, respectively, 0.90 and 99 g kg lower grip strength at time 2 ($p < 0.001$ for both).

Note that, even though most of the above findings are presented in terms of association between lower levels in time 1 and a change (increase or decrease) in time 2, these are equivalent to the same amount of associations between increase in time 1 and an appropriate change in time 2, as long as the direction (positive/negative) of association is unchanged. (Positive association is when both variables increase and decrease together; negative association is when one variable increases, and the other decreases, and vice-versa.)

4. Discussion

We have estimated the relationship between physiologic precursors and phenotypic components of frailty in a population of older adults over a period of 12 years when the components of frailty may be in the process of worsening. Worsening of these components lead to development of frailty. As a result, our estimated relationships are realistic representation of mechanisms of development of frailty. In this community-dwelling population of older adults, we found evidence for a feed-forward loop relationship between appendicular lean mass and grip strength.

Furthermore, we found an even greater feed-forward loop relationship between appendicular lean mass (and lean/fat mass ratio), grip strength, and lower extremity performance. Specifically, we found that appendicular lean mass contributed directly and indirectly to grip strength and the timing in Timed “Up and Go” test (TUG) and that both grip strength and TUG influence future values of appendicular lean mass, suggesting co-regulation of all three variables cross-sectionally and over time. These variables are all components of and precursors to frailty, and their FFL relation provide valuable insight on how frailty develops.

In two of our analyses, a decrease in TUG is found to be in association with an increase in grip strength. This suggests that these variables are coregulated. A decrease a TUG, a measure of lower extremity performance, may increase ability to perform physical activities, which in turn may increase grip strength, a measure of upper extremity strength.

The results of this study provide evidence for FFL relationships in physiological systems and potential for understanding how the characteristics of frailty are related to each other. These findings provide additional evidence that feedback mechanisms are integral in the process of development of frailty. Moreover, it provides empirical evidence of interactions between physiologic and phenotypic measures, such that changes in physiologic measures (e.g. muscle mass) at one point in time may mediate changes in the phenotypic measures (e.g. grip strength) at a later time point. These data support our hypothesis that frailty is due to multi-system dysregulation of a complex dynamical system that has many positive and negative feedback loops critical to maintaining homeostasis.

These results support and expand on our previous findings (RoyChoudhury et al., 2014). Among 436 women in the Women’s Health and Aging Study II (WHAS II), there were feed-forward loops between physical performance and physical activity, suggesting that feedback mechanisms are important between components of the frailty phenotype (RoyChoudhury et al., 2014). In WHAS, we detected a feed-forward loop between grip strength and self-reported physical activity levels (measured in units of hour/day or kcal/day), such that lower grip strength and physical activity at time 1 is associated with lower physical activity at time 2. Here, we detected in a different cohort, of both men and women, similar feed-forward loops between grip-strength, measures of speed and measures of body composition, which added to our previous findings. The two results together suggest the possibility of existence of a larger feed-forward loop between strength, physical activity, fitness and body composition. Further study is required to investigate existence of such loops among components of frailty.

It has been well established that body composition characteristics

affect strength and mobility. This work uses such well understood pairwise relationships to establish validity of a novel method. The novel method evaluates interactions of three measures within a likely complex system of mutual regulatory effects essential to resilience. The biologic plausibility of the findings strengthen the evidence that this method could be useful in probing such systems further. Beyond that, this provides initial supporting evidence that the phenotype and clinical syndrome of frailty results from the dysregulation of multiple regulatory systems that mutually affect each other in a complex adaptive system that maintains robustness of the human organism and resulting resilience.

These findings are the next step forward from our previous findings; here we establish existence of a feed-forward loop encompassing physical activity, physical performance, as well as body composition, in a combined data of older women and men. Thus, we are closer to our goal of a system-wide understanding of how frailty develops. Moreover, previous findings were from data on older women only. Here we extend those findings on data from both older women and men.

Note that we have assumed that the effects of multiple systems is additive. In other words, we have assumed that the effects of multiple systems add to up affect a system at a future time. (For example, effects of strength (measured as grip strength) and body composition (measured as appendicular lean mass) add up to affect body composition at a future time. This is the simplest of assumptions as far as model building is concerned, and we have found evidence for significant feedback mechanism assuming additivity.

We believe that the FFL analysis better models the true underlying biology of aging and frailty that prior approaches. Our use of feed-forward loop analyses using structural equation modeling provides added advantage compared to standard regression models. In standard regression, the causal effects are presumed to be unidirectional, so that no two variables affect each other. For instance, a model could include equations for either X→Y or Y→X, but not both. Many biologic phenomena, however, are bidirectional (or reciprocal), i.e. X⟵→Y. Reciprocal paths, also known as feedback loops, occur when (i) X affects Y at a later time ($X_t \rightarrow Y_{t+1}$); (ii) Y affects X at a later time ($Y_t \rightarrow X_{t+1}$); additionally, (iii) X may affect itself at a later time ($X_t \rightarrow X_{t+1}$); and/or (iv) Y may affect itself at a later time ($Y_t \rightarrow Y_{t+1}$). These reciprocal paths may have cycles of mutual influence (e.g. relation between parental behavior and child behavior, rates of incarceration and crime rates etc.) and sets of variables can be specified to affect each other.

Understanding feed-forward loops provides insights into how multiple systems jointly affect each other and contribute to development of frailty as a dysregulated dynamical system. For example, a reduction in physical activity would not only degrade muscle mass and physical performance, but it would reduce the ability to participate in physical activity at a later time through declining mass and/or physical performance. In other words, a change in a given system comes back to influence the same system at a future time, through its influence of a different system. This mechanism has a number of implications.

A scientific implication of this loop mechanism is that each of these components not only affects frailty unidirectionally, but their relationship has a complex loop structure. The complex loop structure points to the fact that frailty itself is a manifestation of mutual dysregulation between physiologic systems.

These findings are of importance not only because of what they reveal by themselves (that there are feed-forward relationships between different systems), but also because these models are first steps towards creating a system map of the development of frailty. Such a system map, if developed, may provide understanding of which systems are major drivers of what constitutes a critical mass of dysregulation in development of frailty, as based on creation of targeted intervention to prevent frailty.

Another scientific implication of the loop mechanism is that we have the ability to examine whether one variable may have a stronger effect in the loop compared to other variables. For example, FFL analyses may help identify which of the components of the frailty phenotype (weakness, slowness, physical inactivity, weight loss, and exhaustion) and/or a frailty physiotype (muscle mass, fat mass, hormone dysregulation, insulin resistance, and inflammation) is more important in the development of frailty.

Even though we do not have information in this study about how many of the subjects manifested the full frailty phenotype, all of the subjects were older (60+ at baseline). Thus, our data are representative of a cohort where frailty usually manifests. In the cohort, our study investigated how precursive components of frailty interact with each other. The relationship we inferred from studying these components offers etiologic insight because it portrays mechanisms of initial development of frailty (through the interrelations between its precursor components), in a cohort where the likelihood of frailty is increasing. Prior work has demonstrated in a different cohort of older women that initial manifestations of the frailty phenotype are, in 90 percent, diminished grip strength, physical activity and/or walking speed (Xue et al., 2011, 2010).

The ability to identify the strongest component has clinical implications for geriatric care since we may be able to identify component systems that have the largest impact and are most amenable to interventions. Identification of such component systems are important in prevention and treatment of frailty. Once such a component system has been identified, targeted intervention could be used to improve the functionality of that component system. This could not only improve functionality of that component, but it may also improve the other component systems through the strong influence of the first component. Using this type of intervention, potentially in combination with key other components, it may be possible to prevent, treat or reverse the frailty syndrome.

Declaration of Competing Interest

Authors have no competing interests to declare.

References

Bandeen-Roche, K., Xue, Q.-L., Ferrucci, L., Walston, J., Guralnik, J.M., Chaves, P., Zeger, S.L., Fried, L.P., 2006. Phenotype of frailty: characterization in the Women's Health and Aging Studies. J. Gerontol. A Biol. Sci. Med. Sci. 61 (3), 262–266.

Barzilay, J.I., Cotsonis, G.A., Walston, J., Schwartz, A.V., Satterfield, S., Miljkovic, I., Harris, T.B., Health ABC Study, 2009. Insulin resistance is associated with decreased quadriceps muscle strength in nondiabetic adults aged &or = 70 years. Diabetes Care 32 (4), 736–738.

Cappola, A.R., Xue, Q.-L., Fried, L.P., 2009. Multiple hormonal deficiencies in anabolic hormones are found in frail older women: the Women's Health and Aging Studies. J. Gerontol. A Biol. Sci. Med. Sci. 64 (2), 243–248.

Castillo, E.M., Goodman-Gruen, D., Kritz-Silverstein, D., Morton, D.J., Wingard, D.L., Barrett-Connor, E., 2003. Sarcopenia in elderly men and women. Am. J. Prev. Med. 25 (3), 226–231.

Cawthon, P.M., Marshall, L.M., Michael, Y., Dam, T.T., Ensrud, K.E., Barrett-Connor, E., Orwoll, E.S., Osteoporotic Fractures in Men Research Group, 2007. Frailty in older men: prevalence, progression, and relationship with mortality. J. Am. Geriatr. Soc. 55 (8), 1216–1223.

Cohen, A.A., Milot, E., Yong, J., Seplaki, C.L., Fülöp, T., Bandeen-Roche, K., Fried, L.P., 2013. A novel statistical approach shows evidence for multi-system physiological dysregulation during aging. Mech. Ageing Dev. 134 (3–4), 110–117.

Fried, L.P., Tangen, C.M., Walston, J., Newman, A.B., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W.J., Burke, G., McBurnie, M.A., 2001. Frailty in older adults: evidence for a phenotype. J. Gerontol. A Biol. Sci. Med. Sci. 56 (3), M146–M156.

Fried, L.P., Xue, Q.L., Cappola, A.R., Ferrucci, L., Chaves, P., Varadhan, R., Guralnik, J.M., Leng, S.X., Semba, R.D., Walston, J.D., Blaum, C.S., Bandeen-Roche, K., 2009. Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. J. Gerontol. A Biol. Sci. Med. Sci. 64 (October (10)), 1049–1057.

González-Fernández, M., Humbert, I., Winegrad, H., Cappola, A.R., Fried, L.P., 2014. Dysphagia in old-old women: prevalence as determined according to self-report and the 3-ounce water swallowing test. J. Am. Geriatr. Soc. 62 (April (4)), 716–720.

Härkönen, R., Piirtomaa, M., Alaranta, H., 1993. Grip strength and hand position of the dynamometer in 204 Finnish adults. J. Hand Surg. 18 (1), 129–132.

Herman, T., Giladi, N., Hausdorff, J.M., 2011. Properties of the' timed up and go' test: more than meets the eye. Gerontology 57 (3), 203–210.

Kalyani, R.R., Varadhan, R., Weiss, C.O., Fried, L.P., Cappola, A.R., 2012a. Frailty status and altered glucose-insulin dynamics. J. Gerontol. A Biol. Sci. Med. Sci. 67 (12),

1300–1306.
Kalyani, R.R., Varadhan, R., Weiss, C.O., Fried, L.P., Cappola, A.R., 2012b. Frailty status and altered dynamics of circulating energy metabolism hormones after oral glucose in older women. J. Nutr. Health Aging 16 (August (8)), 679–686.
Makary, M.A., Segev, D.L., Pronovost, P.J., Syin, D., Bandeen-Roche, K., Patel, P., Takenaga, R., Devgan, L., Holzmueller, C.G., Tian, J., Fried, L.P., 2010. Frailty as a predictor of surgical outcomes in older patients. J. Am. Coll. Surg. 210 (6), 901–908.
Morley, J.E., Vellas, B., van Kan, G.A., Anker, S.D., Bauer, J.M., Bernabei, R., Cesari, M., Chumlea, W.C., Doehner, W., Evans, J., Fried, L.P., Guralnik, J.M., Katz, P.R., Malmstrom, T.K., McCarter, R.J., Gutierrez Robledo, L.M., Rockwood, K., von Haehling, S., Vandewoude, M.F., Walston, J., 2013. Frailty consensus: a call to action. J. Am. Med. Dir. Assoc. 14 (6), 392–397.
RoyChoudhury, A., Dam, T.L., Varadhan, R., Xue, Q.-L., Fried, L.P., 2014. Analyzing feed-forward loop relationship in aging phenotypes: physical activity and physical performance. Mech. Ageing Dev. 141–142, 5–11.
Salamone, L.M., Fuerst, T., Visser, M., Kern, M., Lang, T., Dockrell, M., Cauley, J.A., Nevitt, M., Tylavsky, F., Lohman, T.G., 2000. Measurement of fat mass using DEXA: a validation study in elderly adults. J. Appl. Physiol. 89 (1), 345–352.
Semba, R.D., Bartali, B., Zhou, J., Blaum, C., Ko, C.W., Fried, L.P., 2006. Low serum micronutrient concentrations predict frailty among older women living in the community. J. Gerontol. A Biol. Sci. Med. Sci. 61 (6), 594–599.
Varadhan, R., Seplaki, C.L., Xue, Q.L., Bandeen-Roche, K., Fried, L.P., 2008. Stimulus-response paradigm for characterizing the loss of resilience in homeostatic regulation associated with frailty. Mech. Ageing Dev. 129 (11), 666–670.
Visser, M., Fuerst, T., Lang, T., Salamone, L., Harris, T.B., 1999. Validity of fan-beam dual-energy X-ray absorptiometry for measuring fat-free mass and leg muscle mass. Health, Aging, and Body Composition Study–Dual-Energy X-ray Absorptiometry and Body Composition Working Group. J. Appl. Physiol. 87 (4), 1513–1520.
Walston, J., McBurnie, M.A., Newman, A., Tracy, R.P., Kop, W.J., Hirsch, C.H., Gottdiener, J., Fried, L.P., Cardiovascular Health Study, 2002. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. Arch. Intern. Med. 162 (20), 2333–2341.
Xue, Q.L., Walston, J.D., Fried, L.P., Beamer, B.A., 2011. Prediction of risk of falling, physical disability, and frailty by rate of decline in grip strength: the women's health and aging study. Arch. Intern. Med. 171 (June (12)), 1119–1121.
Xue, Q.L., Beamer, B.A., Chaves, P.H., Guralnik, J.M., Fried, L.P., 2010. Heterogeneity in rate of decline in grip, hip, and knee strength and the risk of all-cause mortality: the Women's Health and Aging Study II. J. Am. Geriatr. Soc. 58 (November (11)), 2076–2084.