PLOS ONE

RESEARCH ARTICLE

Frailty does not cause all frail symptoms: United States Health and Retirement Study

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Citation: Chao Y-S, Wu C-J, Po JYT, Huang S-Y, Wu H-C, Hsu H-T, et al. (2022) Frailty does not cause all frail symptoms: United States Health and Retirement Study. PLoS ONE 17(11): e0272289. https://doi.org/10.1371/journal.pone.0272289

Editor: George Vousden, Public Library of Science, UNITED KINGDOM

Received: October 21, 2021

Accepted: July 15, 2022

Published: November 2, 2022

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pone.0272289

Data Availability Statement: The HRS data produced by the RAND Center for the Study of Aging can be accessed via the University of Michigan site (https://hrs.isr.umich.edu/data-

Abstract

Background

Frailty is associated with major health outcomes. However, the relationships between frailty and frailty symptoms haven't been well studied. This study aims to show the associations between frailty and frailty symptoms.

Methods

The Health and Retirement Study (HRS) is an ongoing longitudinal biannual survey in the United States. Three of the most used frailty diagnoses, defined by the Functional Domains Model, the Burden Model, and the Biologic Syndrome Model, were reproduced according to previous studies. The associations between frailty statuses and input symptoms were assessed using odds ratios and correlation coefficients.

Results

The sample sizes, mean ages, and frailty prevalence matched those reported in previous studies. Frailty statuses were weakly correlated with each other (coefficients = 0.19 to 0.38, $p < 0.001$ for all). There were 49 input symptoms identified by these three models. Frailty statuses defined by the three models were not significantly correlated with one or two symptoms defined by the same models ($p > 0.05$ for all). One to six symptoms defined by the other two models were not significantly correlated with each of the three frailty statuses ($p > 0.05$ for all). Frailty statuses were significantly correlated with their own bias variables ($p < 0.05$ for all).

Conclusion

Frailty diagnoses lack significant correlations with some of their own frailty symptoms and some of the frailty symptoms defined by the other two models. This finding raises questions

products). The authors do not have special access to the HRS data.

Funding: This study was supported by Taipei Veterans General Hospital in the form of a grant awarded to WCC (V111B-024). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding was received for this study.

Competing interests: YSC is employed by the Canadian Agency for Drugs and Technologies in Health. YSC conducted this study as an independent researcher out of academic curiosity without any material support. The funding agency had no role in this study. This study is not associated with any patents, products in development or marketed products. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

like whether the frailty symptoms lacking significant correlations with frailty statuses could be included to diagnose frailty and whether frailty exists and causes frailty symptoms.

Introduction

Frailty is a syndrome and can be diagnosed with composite criteria that consist of various frailty symptoms [1–3]. Frailty is often characterized by age-related symptoms, such as declines in physical and cognitive functioning. It has been considered significant for the prediction of major health outcomes, such as falls, surgical outcomes, and mortality [2, 3]. By aggregating information from multiple symptoms, frailty index scores can be assigned to individuals [2, 3]. Frailty status can then be derived by applying theoretical thresholds to frailty index scores [2, 3]. Three of the most commonly used frailty indices require 4 to 70 input domains or symptoms for the diagnosis of frailty [2].

Ideally, pathological changes or underlying health conditions are expected to cause or lead to significant increases in symptom occurrence. The increased frequency of symptom development can be used to make diagnoses that serve as proxy measures to the pathological changes {please add new reference: DOI:10.1038/s41598-022-14826-2}. For example, frailty has been recognized as a cause of disability, independent of clinical conditions [4]. Other researchers also found that frailty can lead to symptoms, particularly mental symptoms [5, 6] and fatigue [7]. Frailty has been confirmed using multiple frailty symptoms and considered a diagnosis that represent low physical reserve [8]. However, the effects of frailty on the development of frailty symptoms (those used to diagnose frailty) have not been well discussed. Instead, frailty has been described and defined differently [1]. Some studies have shown that how frailty is diagnosed seems far from ideal and lacks pathological confirmation [2]. Additionally, researchers have confirmed notable differences in the frail patients identified between the three frailty models [1].

In other words, whether frailty causes frailty symptoms remains unclear and whether frailty should cause frailty symptoms has not been explicitly declared in various, often conflicting, theories of frailty [2]. Causal relationships can be established through different approaches [9], such as using the Bradford-Hill Criteria [10]. Among all requirements in the Bradford-Hill Criteria, the strengths of associations between frailty and frailty symptoms are important and can be used to assess the impact of frailty prevention programs on frailty treatment and to understand the mechanisms that cause frailty. For example, it has been suggested that cognitive impairment plays an important role for frailty diagnosis and mortality among frail patients [3]. The confirmation of the causal relationship between frailty and cognitive function has the potential for intervention development. Without extensive reviews of the relationships between frailty and its symptoms, how frailty may influence frailty symptoms is an important question that is left unanswered. This study aims to assess the effect of frailty on the occurrence of frailty symptoms using a cohort that have been used to compare three of the most used frailty indices.

Methods

The Health and Retirement Study (HRS) follows Americans aged 50 years and over every 2 years [1, 2, 11, 12]. The 2004 wave HRS data were used to compare frailty indices defined by 3 models: the Functional Domains Model by Strawbridge et al. [13], the Burden Model by Rockwood et al. [14, 15], and the Biologic Syndrome Model by Fried et al. [4]. Frailty symptoms or

input variables were used to defined various domains defined by the 3 models [2, 3, 16]. When individuals presented enough numbers of frailty symptoms in a domain, these individuals might be considered to have a deficit in this domain for the Functional Domain Model and the Biologic Syndrome Model [2]. For example, the weight loss domain in the Biologic Syndrome Model asked individuals whether they had body mass index (BMI) less than 18.5 kg/m^2 or whether they lost weight for 10% or more, compared to two years ago [1]. This domain required information on weights, heights, BMI, and weights two years ago [1].

In the Burden Model, one symptom represented a single domain and the presence of a symptom suggested the occurrence of a deficit [1, 2]. The frailty indices were the numbers of deficits identified using 4, 70, and 5 domains defined by the 3 frailty models, respectively [1]. Frailty statuses could be diagnosed when individuals had 2, 18 (70 times 0.25), or 3 deficits according to the 3 models, respectively [2]. The details of the frailty symptoms and input variables were published elsewhere (https://doi.org/10.1371/journal.pone.0197859.s002) [2]. The names and definitions of the input variables, frailty symptoms, and domains are listed in Tables 1–3. There were 10, 26, and 14 variables (frailty symptoms, input variables, or domains) identified for the 3 models, respectively. In total, there were 57 variables required to produce the frailty indices defined by the 3 models. In addition, there were 4 bias variables induced by the 4 domains in the Functional Domains Model (Table 1), 1 bias variable induced by the Burden Model (Table 2), and 4 bias variables induced by the Biologic Syndrome Model (Table 3) [2].

Statistical analyses

The associations between the frailty statuses and their frailty symptoms were determined with odds ratios and correlation coefficients. Odds ratios were the ratios of the odds of developing symptoms occurred among frail individuals, compared to the odds among those not frail [17]. Odds ratios were applicable to binomial variables [17]. Odds ratios equaling 1 suggest that the two groups have similar risks of developing symptoms [17]. The processing to transform non-binomial variables to binomial variables were according to the recommendations by the authors of the Burden Model [18]. Pearson's correlation coefficients were used to assess the associations between frailty statuses defined by the 3 models and frailty symptoms or input variables or domains or bias variables [19]. Correlation coefficients ranged from -1 to 1, representing completely opposite information and identical information between 2 variables, respectively. We hypothesized that 1) frailty statuses were not associated with symptom incidence (odds ratio = 1); 2) frailty statuses were not correlated with frailty symptoms or input variables of the frailty indices (correlation coefficient = 0). Correlation coefficients between 0 and 0.10, 0.10 and 0.39, 0.40 and 0.69, 0.70 and 0.89, and 0.90 and 1.00 were interpreted as negligible, weak, moderate, strong, and very strong correlations, respectively [20]. P values were adjusted for multiple comparison using false discovery rates [21]. Two-tailed P values that were less than 0.05 were considered statistically significant. All statistical analyses were conducted within R environment (v4.0.4) [22] and RStudio (v1.4.1106) [23]. This secondary data analysis was approved by the ethics review committee at the Centre Hospitalier de l'Université de Montréal.

Results

There were 11,113, 7,713, and 1,642 HRS participants analyzed for the frailty indices defined by the Functional Domains Model, the Burden Model, and the Biologic Syndrome Model in Tables 1–3, respectively [2]. The numbers of frail patients were 3,059 (27.53%), 3,442 (44.63%), and 203 (12.36%), respectively [2]. The mean ages were 74.92, 78.43, and 77.05 years, respectively. The proportions of females were 57.46%, 58.78%, and 54.69%, respectively.

Table 1. Frailty status defined by the Functional Domains Model and its associations with frailty symptoms.

HRS variables	Definitions	N with symptoms for binomial variables	Odds ratios (95% CIs	Mean (SD)	Correlation coefficients (95% CIs)
r7agey_b	Age at interview (years)			73.92 (7.59)	0.26 (0.24 to 0.27)***
r7bmi	Self-reported body mass index = kg/m2			26.68 (5.31)	-0.02 (-0.04 to 0)
r7cogtot	Total cognition summary score			20.53 (6.08)	-0.41 (-0.42 to -0.39)***
r7dizz	Physical functioning: Dizziness as persistent problem	1577	7.9 (7.03 to 8.87)***	0.14 (0.35)	0.36 (0.35 to 0.38)***
r7eye	Sensory problems: Fair or poor eyesight despite use of corrective lenses			2.95 (1.01)	0.44 (0.42 to 0.45)***
r7fall	fallen down last 2 years			0.9 (2.88)	0.29 (0.27 to 0.31)***
r7frailim1	Frailty index: Functional Domains Model			0.98 (0.93)	0.85 (0.84 to 0.85)***
r7frailim1cat	Frailty status: Functional Domains Model (outcome of this table)	3059	Not applicable	0.28 (0.45)	1 (1 to 1)***
r7hear	Sensory problems: fair or poor hearing despite use of hearing aides			2.87 (1.12)	0.37 (0.35 to 0.39)***
r7lift	some difficulty in lift/carry 10lbs	3631	8.85 (8.05 to 9.72)***	0.33 (0.47)	0.46 (0.45 to 0.48)***
r7memopr	Proxy memory rating			1.39 (1.18)	0.33 (0.31 to 0.35)***
r7wchange	Weight in wave 2002 minus weight in wave 2004 (%)			0.01 (0.08)	-0.04 (-0.05 to -0.02)***
ragender	Male = 0; female = 1	6385	1.32 (1.21 to 1.44)***	0.57 (0.49)	0.06 (0.04 to 0.08)***
Domains and other frailty symptoms identified by the other 2 models					
r7actsum	Summary scores of physical activities			33.45 (9.11)	0.31 (0.29 to 0.33)***
r7arthrcat	Binomial: Arthritis	7693	1.84 (1.67 to 2.03)***	0.69 (0.46)	0.12 (0.1 to 0.14)***
r7bathcat	Binomial: Problems with bathing	1264	8.28 (7.27 to 9.42)***	0.11 (0.32)	0.34 (0.32 to 0.36)***
r7cancrcat	Binomial: Malignant disease	1978	1.03 (0.92 to 1.15)	0.18 (0.38)	0.01 (-0.01 to 0.02)
r7cogimpair	Impaired cognition based on performance-based scores or proxy assessment	999	23.09 (19.14 to 27.85)***	0.09 (0.29)	0.41 (0.4 to 0.43)***
r7deprescat	Binomial: Feeling sad, blue, depressed	2011	3.54 (3.2 to 3.91)***	0.18 (0.39)	0.24 (0.22 to 0.26)***
r7diabscat	Binomial: History of diabetes mellitus	292	1.38 (1.08 to 1.77)*	0.03 (0.16)	0.02 (0.01 to 0.04)**
r7dresscat	Binomial: problem getting dressed	1419	6.01 (5.34 to 6.76)***	0.13 (0.33)	0.31 (0.29 to 0.32)***
r7effort	everything an effort	2932	3.96 (3.62 to 4.34)***	0.26 (0.44)	0.29 (0.27 to 0.31)***
r7fall_cat1	More than 1 falls	3640	3.6 (3.3 to 3.93)***	0.33 (0.47)	0.28 (0.26 to 0.3)***
r7fall_cat2	More than 2 falls	1929	6.71 (6.04 to 7.46)***	0.17 (0.38)	0.36 (0.35 to 0.38)***
r7frail1_1	Dizziness as persistent problem, > = 2 falls in previous 2 years, or difficulty lifting 10 pounds	4383	27.81 (24.63 to 31.42)***	0.39 (0.49)	0.61 (0.6 to 0.62)***
r7frail1_2	Weight in wave 2002 minus weight in wave 2004! 10% of weight in wave 2002 or body mass index o18.5 kg/m2	866	9.35 (7.97 to 10.96)***	0.08 (0.27)	0.3 (0.29 to 0.32)***

(*Continued*)

Table 1. (Continued)

HRS variables	Definitions	N with symptoms for binomial variables	Odds ratios (95% CIs	Mean (SD)	Correlation coefficients (95% CIs)
r7frail1_3	Mild to severe cognitive impairment on performance-based measure or according to proxy and interviewer rating			0.09 (0.29)	0.42 (0.4 to 0.43)***
r7frail1_4	Fair or poor eyesight despite use of corrective lenses or fair or poor hearing despite use of hearing aides			0.42 (0.49)	0.59 (0.58 to 0.6)***
r7frail3_2	Yes to either of two CES-D items: (i) Felt that everything I did was an effort in last week. (ii) Could not get going in last week.	4025	3.99 (3.66 to 4.35)***	0.36 (0.48)	0.3 (0.29 to 0.32)***
r7frail3_3	Frequency of three intensities of activity, lowest quintile (stratified according to sex)	2872	4.11 (3.75 to 4.51)***	0.26 (0.44)	0.3 (0.28 to 0.32)***
r7frail3_4	Time to walk 8 ft, converted to time to walk 15 ft. Cutoff criteria according to sex and height remain the same	5474	1.44 (1.33 to 1.57)***	0.49 (0.5)	0.08 (0.06 to 0.1)***
r7frail3_5	Grip strength: Weakest 20% (stratified according to sex and BMI)	2529	1.43 (1.3 to 1.57)***	0.23 (0.42)	0.07 (0.05 to 0.09)***
r7frailim1	Frailty index: Functional Domains Model			0.98 (0.93)	0.85 (0.84 to 0.85)***
r7frailim2	Frailty index: Burden Model			5.02 (2.83)	0.46 (0.44 to 0.47)***
r7frailim2cat	Frailty status: Burden Model			0.45 (0.5)	0.38 (0.36 to 0.4)***
r7frailim3	Frailty index: Biologic Syndrome Model			1.14 (1.08)	0.35 (0.3 to 0.39)***
r7frailim3cat	Frailty status: Biologic Syndrome Model			0.12 (0.33)	0.3 (0.26 to 0.34)***
r7going	Could not get going	2682	3.41 (3.11 to 3.73)***	0.24 (0.43)	0.25 (0.24 to 0.27)***
r7grip	Grip strength, largest value			30.19 (16.32)	-0.07 (-0.09 to -0.06)***
r7gripl	Grip strength, left hand			26.63 (16.29)	-0.07 (-0.09 to -0.05)***
r7gripr	Grip strength, right hand			28.74 (16.14)	-0.1 (-0.12 to -0.08)***
r7headac	Headache	817	3.05 (2.64 to 3.53)***	0.07 (0.26)	0.15 (0.13 to 0.17)***
r7heartcat	Binomial: Cardiac problems	3631	2.15 (1.97 to 2.35)***	0.33 (0.47)	0.17 (0.15 to 0.18)***
r7height	Self-reported height in meters			1.68 (0.1)	-0.09 (-0.11 to -0.07)***
r7hibp	had high blood pressure since last interview	6791	1.49 (1.36 to 1.62)***	0.61 (0.49)	0.08 (0.07 to 0.1)***
r7ltactx	Frequency of light physical activity			2.87 (1.2)	0.29 (0.28 to 0.31)***
r7lungcat	Binomial: Lung problems	1345	2.02 (1.79 to 2.27)***	0.12 (0.33)	0.11 (0.09 to 0.13)***
r7mdactx	Frequency of moderate physical activity			3.13 (1.37)	0.29 (0.27 to 0.31)***
r7memryscat	Binomial: Memory changes	345	7.46 (5.86 to 9.48)***	0.03 (0.17)	0.18 (0.16 to 0.2)***
r7mobila	Some difficulty in mobility /05			1.36 (1.59)	0.43 (0.42 to 0.45)***
r7muscle	Musculoskeletal problems	386	1.3 (1.05 to 1.62)*	0.03 (0.18)	0.02 (0 to 0.04)*
r7psychcat	Binomial: Depression	1799	2.82 (2.55 to 3.13)***	0.16 (0.37)	0.19 (0.17 to 0.21)***
r7psychscat	Binomial: Changes in general mental functioning	246	3.6 (2.78 to 4.64)***	0.02 (0.15)	0.1 (0.08 to 0.12)***

(*Continued*)

Table 1. (Continued)

HRS variables	Definitions	N with symptoms for binomial variables	Odds ratios (95% CIs	Mean (SD)	Correlation coefficients (95% CIs)
r7seizure	Seizures, generalized	Not available			
r7sleeprcat	Binomial: Sleep changes	3102	2.26 (2.07 to 2.47)***	0.28 (0.45)	0.17 (0.15 to 0.19)***
r7strokcat	Binomial: Cerebrovascular problems	1139	3.36 (2.97 to 3.81)***	0.1 (0.3)	0.19 (0.17 to 0.21)***
r7strokecat	Binomial: History of stroke	1283	3.39 (3.01 to 3.82)***	0.12 (0.32)	0.2 (0.18 to 0.22)***
r7stroks	Had stroke since last interview	255	3.31 (2.58 to 4.25)***	0.02 (0.15)	0.09 (0.08 to 0.11)***
r7tired	Tiredness all the time	1	Not applicable	0 (0.01)	-0.01 (-0.02 to 0.01)
r7toiltcat	Binomial: Toileting problems	903	6.9 (5.95 to 8)***	0.08 (0.27)	0.27 (0.26 to 0.29)***
r7underw	Underweight in wave 2004 (%)	313	7.94 (6.15 to 10.25)***	0.03 (0.17)	0.18 (0.16 to 0.19)***
r7urine	Urinary incontinence	2710	2.35 (2.15 to 2.58)***	0.24 (0.43)	0.18 (0.16 to 0.19)***
r7vgactx	Frequency of vigorous physical activity			4.24 (1.24)	0.2 (0.18 to 0.22)***
r7walkt	Slowness: Time to walk 8 ft, converted to time to walk 15 ft. Cutoff criteria according to sex and height remain the same			5.09 (19.08)	0.11 (0.1 to 0.13)***
r7walkt15	Time to walk 15 feet			9.54 (35.77)	0.11 (0.1 to 0.13)***
r7weight	Self-reported weight in kilograms			76.03 (17.43)	-0.06 (-0.08 to -0.04)***
Bias variables					
Biases induced by the Functional Domains Model					
r7frail1_1res	Bias induced by Dizziness as persistent problem, > = 2 falls in previous 2 years, or difficulty lifting 10 pounds			0 (0.29)	0.35 (0.34 to 0.37)***
r7frail1_2res	Bias induced by Weight in wave 2002 minus weight in wave 2004! 10% of weight in wave 2002 or body mass index o18.5 kg/m2			0 (0.25)	0.2 (0.19 to 0.22)***
r7frail1_3res	Bias induced by Mild to severe cognitive impairment on performance-based measure or according to proxy and interviewer rating			0 (0.15)	-0.03 (-0.05 to -0.01)**
r7frail1_4res	Bias induced by Fair or poor eyesight despite use of corrective lenses or fair or poor hearing despite use of hearing aides			0 (0.2)	0.02 (0.01 to 0.04)*
Biases induced by the Burden Model					
r7frail2res	Bias induced by Summary of proxy memory rating and total cognition summary score			0 (0.04)	-0.14 (-0.16 to -0.11)***
Biases induced by the Biologic Syndrome Model					
r7frail3_2res	Bias induced by Yes to either of two CES-D items: (i) Felt that everything I did was an effort in last week. (ii) Could not get going in last week.			0 (0.17)	0.01 (-0.04 to 0.06)
r7frail3_3res	Bias induced by Frequency of three intensities of activity, lowest quintile (stratified according to sex)			0 (0.31)	0.1 (0.05 to 0.15)***
r7frail3_4res	Bias induced by Time to walk 8 ft, converted to time to walk 15 ft. Cutoff criteria according to sex and height remain the same			0 (0.49)	0.16 (0.12 to 0.21)***
r7frail3_5res	Bias induced by Grip strength: Weakest 20% (stratified according to sex and BMI)			0 (0.34)	0.05 (0 to 0.09)

n = 11,113; frailty n (%) = 3,059 (27.53%); mean age = 74.92 years; female % = 57.46%.

BMI = body mass index; CES-D = Center for Epidemiological Studies Depression; HRS = Health and Retirement Study.

* = $p < 0.05$

** = $p < 0.01$

*** = $p < 0.001$.

https://doi.org/10.1371/journal.pone.0272289.t001

Frailty symptom development based on frailty status

In Tables 1–3, the associations between frailty status (yes or no) and symptom development are shown using odds ratios and correlation coefficients. Overall, most of frailty symptoms were significantly associated with frailty statuses. However, frailty statuses defined by the three models were not significantly associated with all frailty symptoms or input variables or domains. The frailty symptoms or input variables or domains that were not significantly associated with frailty statuses are described below. The correlation coefficients between the three frailty statuses ranged from 0.19 to 0.38 (weak correlations, $p < 0.001$ for all).

In Table 1, the frailty status defined by the Functional Domains Model was not significantly correlated with one input variable, BMI (correlation coefficients = -0.02, 95% CI = -0.04 to 0).

Among the frailty symptoms or input variables or domains identified by the other two models, two symptoms, malignant disease and tiredness all the time, were not significantly associated with this frailty status (p of correlations > 0.05 for both symptoms). Among the bias variables, one bias variable that was induced by having one of two Center for Epidemiologic Studies Depression (CES-D) items was not significantly associated with this frailty status (correlation $p > 0.05$).

In Table 2, the frailty status defined by the Burden Model was assessed for the associations with frailty symptoms, input variables, and domains. One input symptom, tiredness all the time, was not significantly associated with this frailty status (p of correlation > 0.05). One symptom identified by the other two models, self-reported weight, was not significantly correlated with this frailty status ($p > 0.05$). Among the bias variables, four were not significantly correlated with this frailty status ($p > 0.05$ for all).

In Table 3, the frailty status defined by the Biologic Syndrome Model was assessed for the associations with frailty symptoms, input variables, and domains. BMI was not significantly correlated with this frailty status ($p > 0.05$). Because the values of two symptoms, proxy memory rating and history of stroke, were the same for frail and non-frail HRS participants for this frailty index, their correlations with this frailty status could not be assessed. Six symptoms defined by the other two models, history of malignant disease, diabetes mellitus, headache, memory change, musculoskeletal problems, and change in general mental functioning, were not significantly correlated with this frailty status ($p > 0.05$ for all).

Correlations with bias variables

In Tables 1–3, the correlations with bias variables are shown for the three frailty indices. Each frailty status was significantly associated with the bias variables induced by their own diagnostic criteria. The frailty statuses defined by the Functional Domains Model, the Burden Model, and the Biologic Syndrome Model, were significantly correlated with four, one, and four bias variables induced by their own models, respectively ($p < 0.05$ for all). In addition, the frailty status defined by the Functional Domains Model, the Burden Model, and the Biologic Syndrome Model, were significantly correlated with three, four, and two bias variables induced by the other two models, respectively ($p < 0.05$ for all).

Discussion

Strengths of the associations are one of the Bradford-Hill criteria to assess whether a disease causes symptoms or outcomes [10]. Frailty has been promising in establishing causal relationships with major health outcomes, such as mortality and falls, based on frailty's significant associations with them [2]. However, whether frailty should cause frailty symptoms has not been declared in the theories of frailty and whether frailty causes frailty symptoms have not been well studied. In this study using the HRS data, three of the most used frailty diagnoses fail

Table 2. Frailty status defined by the Burden Model and its associations with frailty symptoms.

HRS variables	Definitions	N with symptoms for binomial variables	Odds ratios (95% CIs	Mean (SD)	Correlation coefficients (95% CIs)
r7agey_b	Age at interview (years)			77.43 (6.46)	0.19 (0.17 to 0.22)***
r7arthrcat	Binomial: Arthritis	5457	4.45 (3.97 to 4.99)***	0.71 (0.45)	0.3 (0.28 to 0.32)***
r7bathcat	Binomial: Problems with bathing	1091	28.44 (21.95 to 36.86)***	0.14 (0.35)	0.4 (0.39 to 0.42)***
r7cancrcat	Binomial: Malignant disease	1489	2.12 (1.89 to 2.38)***	0.19 (0.39)	0.15 (0.13 to 0.17)***
r7cogtot	Total cognition summary score			19.69 (6.27)	-0.25 (-0.27 to -0.23)***
r7deprescat	Binomial: Feeling sad, blue, depressed	1480	5.55 (4.87 to 6.32)***	0.19 (0.39)	0.31 (0.29 to 0.33)***
r7diabscat	Binomial: History of diabetes mellitus	174	3.07 (2.21 to 4.26)***	0.02 (0.15)	0.08 (0.06 to 0.1)***
r7dresscat	Binomial: problem getting dressed	1159	18.97 (15.34 to 23.48)***	0.15 (0.36)	0.4 (0.38 to 0.42)***
r7fall	Fallen down last 2 years			0.99 (2.89)	0.3 (0.28 to 0.32)***
r7frailim2	Frailty index: Burden Model			5.02 (2.83)	0.8 (0.8 to 0.81)***
r7frailim2cat	Frailty status: Burden Model (outcome of this table)	3442	Not applicable	0.45 (0.5)	1 (1 to 1)***
r7headac	Headache	514	5.28 (4.25 to 6.58)***	0.07 (0.25)	0.19 (0.17 to 0.21)***
r7heartcat	Binomial: Cardiac problems	2817	4.01 (3.64 to 4.42)***	0.37 (0.48)	0.32 (0.3 to 0.34)***
r7hibp	Had high blood pressure since last interview	4809	2.81 (2.55 to 3.1)***	0.62 (0.48)	0.24 (0.22 to 0.26)***
r7lungcat	Binomial: Lung problems	928	4.41 (3.77 to 5.16)***	0.12 (0.33)	0.23 (0.2 to 0.25)***
r7memopr	Proxy memory rating			1.45 (1.29)	0.23 (0.21 to 0.25)***
r7memryscat	Binomial: Memory changes	303	5.95 (4.43 to 8)***	0.04 (0.19)	0.15 (0.13 to 0.17)***
r7mobila	Some difficulty in mobility /05			1.51 (1.66)	0.56 (0.55 to 0.58)***
r7muscle	Musculoskeletal problems	258	3.61 (2.73 to 4.78)***	0.03 (0.18)	0.11 (0.09 to 0.13)***
r7psychcat	Binomial: Depression	1230	7.74 (6.63 to 9.04)***	0.16 (0.37)	0.33 (0.31 to 0.35)***
r7psychscat	Binomial: Changes in general mental functioning	188	15.02 (8.84 to 25.5)***	0.02 (0.15)	0.15 (0.13 to 0.17)***
r7seizure	Seizures, generalized	0	Not applicable	0	Not applicable for uniform values
r7sleeprcat	Binomial: Sleep changes	2185	5.05 (4.53 to 5.63)***	0.28 (0.45)	0.35 (0.33 to 0.37)***
r7strokcat	Binomial: Cerebrovascular problems	923	11.45 (9.34 to 14.03)***	0.12 (0.32)	0.32 (0.3 to 0.34)***
r7strokecat	Binomial: History of stroke	1062	10.42 (8.68 to 12.51)***	0.14 (0.34)	0.34 (0.32 to 0.36)***
r7tired	Tiredness all the time	1	Not applicable	0 (0.01)	0.01 (-0.01 to 0.03)
r7toiltcat	Binomial: Toileting problems	759	44.18 (29.79 to 65.52)***	0.1 (0.3)	0.35 (0.33 to 0.36)***

(*Continued*)

Table 2. (Continued)

HRS variables	Definitions	N with symptoms for binomial variables	Odds ratios (95% CIs	Mean (SD)	Correlation coefficients (95% CIs)
r7urine	Urinary incontinence	2075	6.41 (5.71 to 7.19)***	0.27 (0.44)	0.38 (0.36 to 0.4)***
ragender	Male = 0; female = 1	4534	1.69 (1.54 to 1.85)***	0.59 (0.49)	0.13 (0.1 to 0.15)***
Domains and other frailty symptoms identified by the other 2 models					
r7actsum	Summary scores of physical activities			34.44 (8.92)	0.35 (0.33 to 0.37)***
r7bmi	Self-reported body mass index = kg/m2			26.1 (5.07)	0.07 (0.05 to 0.1)***
r7cogimpair	Impaired cognition based on performance-based scores or proxy assessment	884	4.71 (4 to 5.54)***	0.11 (0.32)	0.23 (0.21 to 0.25)***
r7dizz	Physical functioning: Dizziness as persistent problem	1163	3.93 (3.42 to 4.5)***	0.15 (0.36)	0.23 (0.21 to 0.25)***
r7effort	Everything an effort	2153	4.59 (4.12 to 5.11)***	0.28 (0.45)	0.33 (0.31 to 0.35)***
r7eye	Sensory problems: Fair or poor eyesight despite use of corrective lenses			3 (1.03)	0.26 (0.24 to 0.28)***
r7fall_cat1	More than 1 falls	2761	5.61 (5.06 to 6.21)***	0.36 (0.48)	0.39 (0.37 to 0.41)***
r7fall_cat2	More than 2 falls	1499	6.94 (6.06 to 7.95)***	0.19 (0.4)	0.35 (0.33 to 0.37)***
r7frail1_1	Dizziness as persistent problem, > = 2 falls in previous 2 years, or difficulty lifting 10 pounds	3290	6.02 (5.45 to 6.64)***	0.43 (0.49)	0.42 (0.4 to 0.44)***
r7frail1_2	Weight in wave 2002 minus weight in wave 2004! 10% of weight in wave 2002 or body mass index o18.5 kg/m2	635	1.97 (1.67 to 2.32)***	0.08 (0.27)	0.09 (0.07 to 0.11)***
r7frail1_3	Mild to severe cognitive impairment on performance-based measure or according to proxy and interviewer rating			0.11 (0.32)	0.23 (0.21 to 0.25)***
r7frail1_4	Fair or poor eyesight despite use of corrective lenses or fair or poor hearing despite use of hearing aides			0.45 (0.5)	0.22 (0.2 to 0.24)***
r7frail3_2	Yes to either of two CES-D items: (i) Felt that everything I did was an effort in last week. (ii) Could not get going in last week.	2977	4.72 (4.28 to 5.21)***	0.39 (0.49)	0.36 (0.34 to 0.38)***
r7frail3_3	Frequency of three intensities of activity, lowest quintile (stratified according to sex)	2226	4.89 (4.39 to 5.45)***	0.29 (0.45)	0.34 (0.32 to 0.36)***
r7frail3_4	Time to walk 8 ft, converted to time to walk 15 ft. Cutoff criteria according to sex and height remain the same	3853	1.37 (1.25 to 1.5)***	0.5 (0.5)	0.08 (0.06 to 0.1)***
r7frail3_5	Grip strength: Weakest 20% (stratified according to sex and BMI)	1840	1.4 (1.26 to 1.55)***	0.24 (0.43)	0.07 (0.05 to 0.09)***
r7frailim1	Frailty index: Functional Domains Model			1.08 (0.96)	0.43 (0.41 to 0.45)***
r7frailim1cat	Frailty status: Functional Domains Model	2434	5.57 (5.01 to 6.19)***	0.32 (0.46)	0.38 (0.36 to 0.4)***
r7frailim2	Frailty index: Burden Model			5.02 (2.83)	0.8 (0.8 to 0.81)***
r7frailim3	Frailty index: Biologic Syndrome Model			1.22 (1.11)	0.28 (0.23 to 0.33)***
r7frailim3cat	Frailty status: Biologic Syndrome Model			0.14 (0.35)	0.19 (0.14 to 0.24)***
r7going	could not get going	2026	4.64 (4.15 to 5.18)***	0.26 (0.44)	0.32 (0.3 to 0.34)***
r7grip	Grip strength, largest value			29.49 (15.93)	-0.08 (-0.1 to -0.06)***
r7gripl	Grip strength, left hand			25.89 (15.72)	-0.07 (-0.09 to -0.04)***
r7gripr	Grip strength, right hand			27.99 (15.37)	-0.11 (-0.13 to -0.09)***

(*Continued*)

Table 2. (Continued)

HRS variables	Definitions	N with symptoms for binomial variables	Odds ratios (95% CIs	Mean (SD)	Correlation coefficients (95% CIs)
r7hear	Sensory problems: fair or poor hearing despite use of hearing aides			2.97 (1.13)	0.16 (0.14 to 0.18)***
r7height	Self-reported height in meters			1.68 (0.1)	-0.1 (-0.13 to -0.08)***
r7lift	Some difficulty in lift/carry 10lbs	2862	5.88 (5.31 to 6.51)***	0.37 (0.48)	0.4 (0.39 to 0.42)***
r7ltactx	Frequency of light physical activity			2.99 (1.24)	0.3 (0.28 to 0.32)***
r7mdactx	Frequency of moderate physical activity			3.24 (1.41)	0.34 (0.32 to 0.36)***
r7stroks	Had stroke since last interview	208	13 (8.09 to 20.88)***	0.03 (0.16)	0.15 (0.13 to 0.18)***
r7underw	Underweight in wave 2004 (%)	270	1.68 (1.31 to 2.14)***	0.04 (0.18)	0.05 (0.03 to 0.07)***
r7vgactx	Frequency of vigorous physical activity			4.35 (1.19)	0.23 (0.21 to 0.25)***
r7walkt	Slowness: Time to walk 8 ft, converted to time to walk 15 ft. Cutoff criteria according to sex and height remain the same			5.2 (19.49)	0.12 (0.1 to 0.15)***
r7walkt15	Time to walk 15 feet			9.75 (36.55)	0.12 (0.1 to 0.15)***
r7wchange	Weight in wave 2002 minus weight in wave 2004 (%)			0.01 (0.08)	0.04 (0.02 to 0.07)***
r7weight	Self-reported weight in kilograms			73.91 (16.73)	0 (-0.02 to 0.03)
Bias variables					
Bias variables induced by the Functional Domains Model					
r7frail1_1res	Bias induced by Dizziness as persistent problem, > = 2 falls in previous 2 years, or difficulty lifting 10 pounds			0.01 (0.3)	0.19 (0.17 to 0.21)***
r7frail1_2res	Bias induced by Weight in wave 2002 minus weight in wave 2004! 10% of weight in wave 2002 or body mass index o18.5 kg/m2			0 (0.26)	0.15 (0.13 to 0.17)***
r7frail1_3res	Bias induced by Mild to severe cognitive impairment on performance-based measure or according to proxy and interviewer rating			0 (0.17)	-0.01 (-0.03 to 0.01)
r7frail1_4res	Bias induced by Fair or poor eyesight despite use of corrective lenses or fair or poor hearing despite use of hearing aides			0 (0.21)	0.01 (-0.01 to 0.03)
Bias variables induced by the Burden Model					
r7frail2res	Bias induced by Summary of proxy memory rating and total cognition summary score			0 (0.04)	-0.06 (-0.08 to -0.04)***
Bias variables induced by the Biologic Syndrome Model					
r7frail3_2res	Bias induced by Yes to either of two CES-D items: (i) Felt that everything I did was an effort in last week. (ii) Could not get going in last week.			0 (0.17)	-0.04 (-0.09 to 0.01)
r7frail3_3res	Bias induced by Frequency of three intensities of activity, lowest quintile (stratified according to sex)			0 (0.32)	0.12 (0.07 to 0.17)***
r7frail3_4res	Bias induced by Time to walk 8 ft, converted to time to walk 15 ft. Cutoff criteria according to sex and height remain the same			0.03 (0.49)	0.09 (0.03 to 0.14)**
r7frail3_5res	Bias induced by Grip strength: Weakest 20% (stratified according to sex and BMI)			0.01 (0.35)	0.03 (-0.03 to 0.08)

n = 7,713; frailty n (%) = 6,755 (87.58%); mean age = 78.43 years; female % = 58.78%.

BMI = body mass index; CES-D = Center for Epidemiological Studies Depression; HRS = Health and Retirement Study.

* = $p < 0.05$

** = $p < 0.01$

*** = $p < 0.001$.

https://doi.org/10.1371/journal.pone.0272289.t002

Table 3. Frailty status defined by the Biologic Syndrome Model and its associations with frailty symptoms.

HRS	Definitions variables	N with symptoms for binomial variables	Odds ratios (95% CIs	Mean (SD)	Correlation coefficients (95% CIs)
r7agey_b	Age at interview (years)			76.05 (7.36)	0.23 (0.19 to 0.28)***
r7bmi	Self-reported body mass index = kg/m2			26.41 (4.91)	-0.04 (-0.09 to 0.01)
r7cogtot	Total cognition summary score			21.44 (4.79)	-0.22 (-0.26 to -0.17)***
r7effort	Everything an effort	258	5.56 (4.04 to 7.66)***	0.16 (0.36)	0.28 (0.23 to 0.32)***
r7frailim3	Frailty index: Biologic Syndrome Model			1.14 (1.08)	0.73 (0.7 to 0.75)***
r7frailim3cat	Frailty status: Biologic Syndrome Model (outcome of this table)	203	Not applicable	0.12 (0.33)	1 (1 to 1)***
r7going	Could not get going	306	6.43 (4.7 to 8.8)***	0.19 (0.39)	0.31 (0.27 to 0.36)***
r7gripl	Grip strength, left hand			24.85 (13.1)	-0.28 (-0.32 to -0.23)***
r7gripr	Grip strength, right hand			27.38 (13.46)	-0.32 (-0.36 to -0.28)***
r7height	Self-reported height in meters			1.69 (0.1)	-0.12 (-0.17 to -0.08)***
r7mdactx	Frequency of moderate physical activity			2.93 (1.3)	0.41 (0.37 to 0.45)***
r7memopr	Proxy memory rating (1 to 6)			1 (0)	Not applicable for uniform values
r7stroks	had stroke since last interview (1 = no, 2 = yes)			1 (0)	Not applicable for uniform values
r7vgactx	Frequency of vigorous physical activity			4.18 (1.26)	0.21 (0.16 to 0.26)***
r7walkt	Slowness: Time to walk 8 ft, converted to time to walk 15 ft. Cutoff criteria according to sex and height remain the same			4.14 (13.29)	0.42 (0.38 to 0.46)***
ragender	Male = 0; female = 1	898	2.61 (1.88 to 3.64)***	0.55 (0.5)	0.14 (0.1 to 0.19)***
Domains and frailty symptoms identified by the other 2 models					
r7actsum	Summary scores of physical activities			32.41 (8.61)	0.37 (0.33 to 0.41)***
r7arthrcat	Binomial: Arthritis	1140	2.4 (1.63 to 3.52)***	0.69 (0.46)	0.11 (0.06 to 0.16)***
r7bathcat	Binomial: Problems with bathing	88	6.75 (4.3 to 10.59)***	0.05 (0.23)	0.23 (0.18 to 0.28)***
r7cancrcat	Binomial: Malignant disease	300	1.28 (0.89 to 1.83)	0.18 (0.39)	0.03 (-0.02 to 0.08)
r7cogimpair	Impaired cognition based on performance-based scores or proxy assessment	45	5.09 (2.75 to 9.42)***	0.03 (0.16)	0.14 (0.09 to 0.19)***
r7deprescat	Binomial: Feeling sad, blue, depressed	0	Not applicable	0	Not applicable for uniform values
r7diabscat	Binomial: History of diabetes mellitus	42	1.7 (0.77 to 3.72)	0.03 (0.16)	0.03 (-0.02 to 0.08)
r7dizz	Physical functioning: Dizziness as persistent problem	176	2 (1.34 to 2.98)**	0.11 (0.31)	0.09 (0.04 to 0.13)***
r7dresscat	Binomial: problem getting dressed	120	3.64 (2.39 to 5.54)***	0.07 (0.26)	0.16 (0.11 to 0.2)***
r7eye	Sensory problems: Fair or poor eyesight despite use of corrective lenses			2.85 (0.97)	0.13 (0.09 to 0.18)***

(*Continued*)

Table 3. (Continued)

HRS	Definitions variables	N with symptoms for binomial variables	Odds ratios (95% CIs	Mean (SD)	Correlation coefficients (95% CIs)
r7fall	fallen down last 2 years			0.75 (2.34)	0.11 (0.06 to 0.16)***
r7fall_cat1	More than 1 falls	513	2.2 (1.63 to 2.96)***	0.31 (0.46)	0.13 (0.08 to 0.18)***
r7fall_cat2	More than 2 falls	242	2.34 (1.65 to 3.31)***	0.15 (0.35)	0.12 (0.07 to 0.17)***
r7frail1_1	Dizziness as persistent problem, > = 2 falls in previous 2 years, or difficulty lifting 10 pounds	573	3.3 (2.44 to 4.46)***	0.35 (0.48)	0.2 (0.15 to 0.24)***
r7frail1_2	Weight in wave 2002 minus weight in wave 2004! 10% of weight in wave 2002 or body mass index o18.5 kg/m2	94	8.49 (5.49 to 13.14)***	0.06 (0.23)	0.27 (0.23 to 0.32)***
r7frail1_3	Mild to severe cognitive impairment on performance-based measure or according to proxy and interviewer rating	45	5.09 (2.75 to 9.42)***	0.03 (0.16)	0.14 (0.09 to 0.19)***
r7frail1_4	Fair or poor eyesight despite use of corrective lenses or fair or poor hearing despite use of hearing aides	645	2.24 (1.66 to 3.02)***	0.39 (0.49)	0.13 (0.09 to 0.18)***
r7frail3_2	Yes to either of two CES-D items: (i) Felt that everything I did was an effort in last week. (ii) Could not get going in last week.	441	9.93 (7.13 to 13.84)***	0.27 (0.44)	0.38 (0.34 to 0.42)***
r7frail3_3	Frequency of three intensities of activity, lowest quintile (stratified according to sex)	329	17.58 (12.47 to 24.78)***	0.2 (0.4)	0.49 (0.45 to 0.52)***
r7frail3_4	Time to walk 8 ft, converted to time to walk 15 ft. Cutoff criteria according to sex and height remain the same	724	27.06 (14.95 to 48.96)***	0.44 (0.5)	0.38 (0.34 to 0.42)***
r7frail3_5	Grip strength: Weakest 20% (stratified according to sex and BMI)	290	12.72 (9.18 to 17.64)***	0.18 (0.38)	0.44 (0.4 to 0.48)***
r7frailim1	Frailty index: Functional Domains Model			0.83 (0.8)	0.31 (0.26 to 0.35)***
r7frailim1cat	Frailty status: Functional Domains Model	340	5.91 (4.34 to 8.06)***	0.21 (0.41)	0.3 (0.26 to 0.34)***
r7frailim2	Frailty index: Burden Model			4.17 (2.07)	0.27 (0.22 to 0.32)***
r7frailim2cat	Frailty status: Burden Model			0.33 (0.47)	0.19 (0.14 to 0.24)***
r7frailim3	Frailty index: Biologic Syndrome Model			1.14 (1.08)	0.73 (0.7 to 0.75)***
r7grip	Grip strength, largest value			28.31 (13.69)	-0.32 (-0.36 to -0.27)***
r7headac	Headache	74	1.11 (0.56 to 2.2)	0.05 (0.21)	0.01 (-0.04 to 0.06)
r7hear	Sensory problems: fair or poor hearing despite use of hearing aides			2.88 (1.09)	0.11 (0.06 to 0.16)***
r7heartcat	Binomial: Cardiac problems	562	1.83 (1.36 to 2.46)***	0.34 (0.47)	0.1 (0.05 to 0.15)***
r7hibp	Had high blood pressure since last interview	987	1.51 (1.11 to 2.07)**	0.6 (0.49)	0.06 (0.02 to 0.11)**
r7lift	Some difficulty in lift/carry 10lbs	440	6.83 (4.98 to 9.35)***	0.27 (0.44)	0.32 (0.28 to 0.37)***
r7ltactx	Frequency of light physical activity			2.71 (1.06)	0.25 (0.2 to 0.29)***
r7lungcat	Binomial: Lung problems	165	1.84 (1.21 to 2.79)**	0.1 (0.3)	0.07 (0.02 to 0.12)**
r7memryscat	Binomial: Memory changes	20	1.79 (0.59 to 5.4)	0.01 (0.11)	0.03 (-0.02 to 0.07)
r7mobila	Some difficulty in mobility /05			1.12 (1.38)	0.37 (0.33 to 0.41)***
r7muscle	Musculoskeletal problems	57	0.53 (0.19 to 1.47)	0.03 (0.18)	-0.03 (-0.08 to 0.02)

(*Continued*)

Table 3. (Continued)

HRS	Definitions variables	N with symptoms for binomial variables	Odds ratios (95% CIs	Mean (SD)	Correlation coefficients (95% CIs)
r7psychcat	Binomial: Depression	165	2.38 (1.6 to 3.54)***	0.1 (0.3)	0.11 (0.06 to 0.16)***
r7psychscat	Binomial: Changes in general mental functioning	17	1.53 (0.43 to 5.36)	0.01 (0.1)	0.02 (-0.03 to 0.06)
r7seizure	Seizures, generalized	0	Not applicable		Not applicable for uniform values
r7sleeprcat	Binomial: Sleep changes	346	1.74 (1.25 to 2.41)**	0.21 (0.41)	0.08 (0.03 to 0.13)***
r7strokcat	Binomial: Cerebrovascular problems	110	2.65 (1.68 to 4.18)***	0.07 (0.25)	0.11 (0.06 to 0.15)***
r7strokecat	Binomial: History of stroke	139	2.56 (1.68 to 3.88)***	0.08 (0.28)	0.11 (0.06 to 0.16)***
r7tired	Tiredness all the time	0	Not applicable		Not applicable for uniform values
r7toiltcat	Binomial: Toileting problems	60	6.07 (3.56 to 10.35)***	0.04 (0.19)	0.18 (0.14 to 0.23)***
r7underw	Underweight in wave 2004 (%)	36	9.72 (4.95 to 19.09)***	0.02 (0.15)	0.2 (0.15 to 0.24)***
r7urine	Urinary incontinence	360	2.14 (1.56 to 2.94)***	0.22 (0.41)	0.12 (0.07 to 0.17)***
r7walkt15	Time to walk 15 feet			7.76 (24.91)	0.42 (0.38 to 0.46)***
r7wchange	Weight in wave 2002 minus weight in wave 2004 (%)			0 (0.06)	0.05 (0 to 0.1)*
r7weight	Self-reported weight in kilograms			75.75 (16.87)	-0.1 (-0.15 to -0.05)***
Bias variables					
Bias variables induced by the Functional Domains Model					
r7frail1_1res	Bias induced by Dizziness as persistent problem, > = 2 falls in previous 2 years, or difficulty lifting 10 pounds			0 (0.29)	0.03 (-0.02 to 0.08)
r7frail1_2res	Bias induced by Weight in wave 2002 minus weight in wave 2004! 10% of weight in wave 2002 or body mass index o18.5 kg/m2			-0.03 (0.22)	0.21 (0.17 to 0.26)***
r7frail1_3res	Bias induced by Mild to severe cognitive impairment on performance-based measure or according to proxy and interviewer rating			0 (0.16)	-0.02 (-0.06 to 0.03)
r7frail1_4res	Bias induced by Fair or poor eyesight despite use of corrective lenses or fair or poor hearing despite use of hearing aides			0 (0.21)	0 (-0.05 to 0.05)
Bias variables induced by the Burden Model					
r7frail2res	Bias induced by Summary of proxy memory rating and total cognition summary score			0 (0.01)	-0.21 (-0.27 to -0.16)***
Bias variables induced by the Biologic Syndrome Model					
r7frail3_2res	Bias induced by Yes to either of two CES-D items: (i) Felt that everything I did was an effort in last week. (ii) Could not get going in last week.			0 (0.17)	0.08 (0.03 to 0.13)***
r7frail3_3res	Bias induced by Frequency of three intensities of activity, lowest quintile (stratified according to sex)			0 (0.31)	0.34 (0.3 to 0.38)***
r7frail3_4res	Bias induced by Time to walk 8 ft, converted to time to walk 15 ft. Cutoff criteria according to sex and height remain the same			0 (0.49)	0.3 (0.26 to 0.34)***
r7frail3_5res	Bias induced by Grip strength: Weakest 20% (stratified according to sex and BMI)			0 (0.34)	0.26 (0.22 to 0.31)***

n = 1,642; frailty n (%) = 540 (32.89%); mean age = 77.05 years; female % = 54.69s%. HRS = Health and Retirement Study.

BMI = body mass index; CES-D = Center for Epidemiological Studies Depression; HRS = Health and Retirement Study.

* = $p < 0.05$

** = $p < 0.01$

*** = $p < 0.001$.

https://doi.org/10.1371/journal.pone.0272289.t003

to demonstrate significant correlations with some of the frailty symptoms of their own or those defined by the other two frailty diagnoses. When frailty lacks significant associations with frailty symptoms, this suggests frailty diagnoses are made based on so-called frailty symptoms, some of which frailty may not cause them. This needs serious discussion and examination.

Why frailty fails to be significantly associated with frailty symptoms?

Frailty diagnoses do not fully support the models of their own by showing insignificant correlations with some of their own frailty symptoms or input variables. One reason may be that frailty researchers did not recognize the importance of causation between frailty and frailty symptoms. The authors of the Burden Model recommended selecting frailty symptoms based on the associations between the candidate symptoms and two factors: age and general health status [18], rather than selecting the symptoms that cause or are caused by frailty. For this model, the so-called frailty symptoms are, in fact, age-related and general health-related variables.

Second, for the Burden Model that requires a large number of frailty symptoms [18], some symptoms may not present in the population at all and are used for frailty diagnosis regardless. For example, in the HRS cohort, since we did not identify any patients with generalized seizures and it was impossible to determine the association between this symptom and the frailty status defined by this model. Including frailty symptoms that do not present in a population can underestimate the prevalence rate of frailty defined by the Burden Model. This is because the diagnostic threshold of this model is proportional to the total number of frailty symptoms used [18]. When a symptom that should not be included in the diagnostic criteria is included, the diagnostic threshold increases with the total number of frailty symptoms. If the symptom, generalized seizures, is excluded from the diagnostic criteria, the diagnostic threshold can decrease and it is likely that more HRS participants can qualify the diagnosis of frailty defined by the Burden Model.

The third reason is that the diagnostic criteria of frailty have been made so complicated that biases have been introduced and interfered the relationships between frailty and frailty symptoms. The biases are produced by censoring the sum of multiple symptoms and dichotomizing continuous variables [2]. These biases are so important that each of the frailty indices defined by the three models is significantly associated with the biases created by their own or the other two models. In fact, the biases generated by the diagnostic criteria of the Biologic Syndrome Model explain this model's frailty index better than its frailty symptoms [2]. When the frailty indices better represent the biases, these indices are less likely to have significant associations with their frailty symptoms.

The last reason is the correlations between frailty symptoms have been neglected. The correlations between symptoms, symptom prevalence, and the design of the diagnostic criteria (whether biases are created and integrated to the diagnosis) are the three major determinants of the prevalence of the diagnosis [24]. Neglecting the importance of symptom correlations can lead to major errors. For example, when five highly correlated variables with the same means (correlation coefficients = 1) are summed to create an index, this index is not very different from five times any one of the five input variables [25]. When two completely opposite variables with mean values of 0 (correlation coefficient = -1) are summed, the derived index contains only 0 [25]. The frailty indices defined by the three frailty models consist of frailty symptoms of various correlations with each other. Some of the frailty symptoms in the three models may be highly correlated with each other. It takes only four frailty symptoms to explain more than 54% of the variances of the three frailty indices that use 9 or more frailty symptoms

[2]. This issue becomes more problematic for frailty diagnoses made based on a large number of frailty symptoms. The frailty status defined by the Burden Model requires at least 30 symptoms for diagnosis and 70 symptoms have often been used [18]. It took only 11 frailty symptoms to explain more than 90% of the variances of the frailty index [2]. The frailty status defined by this model is not significantly associated with two of its frailty symptoms in this study. The role of insignificant symptoms, seizure and tiredness, in the frailty status defined by the Burden Model haven't been discussed in previous studies [18].

Causation?

In addition to the strengths of associations, the evidence to support the causal relationship between frailty and frailty symptoms seems limited. The pathological changes that are considered related to frailty include sarcopenia, heart disease, and lung disease, depending on the frailty models [2]. In this study, grip strength, cardiac problems, and lung problems were significantly correlated with the three frailty indices, respectively. However, the biological and pathological evidence that support the causal relationship between frailty and the frailty symptoms of the other organ systems seems insufficient [26].

Assumptions

The different patterns of the insignificance between frailty symptoms and the 3 frailty statuses indicated conflicting views on frailty. The 3 frailty models have major discrepancies in the underlying assumptions, including theoretical frameworks, age thresholds, the selection of frailty symptoms, and the design of diagnostic criteria [2]. Subsequently, the differences in these assumptions between frailty models can be shown with the symptoms that best explained frailty statuses [2]. We found the frailty symptoms or input variables that had the largest correlation coefficients with the three frailty statuses were different. The three symptoms that have the largest significant correlation coefficients with the frailty indices defined by the Functional Domain Model, the Burden Model, and the Biologic Syndrome Model are some difficulties in lifting 10 pounds, some difficulty in mobility, and slowness measured by time to walk 8 feet, respectively. The paths from non-frailty to frailty vary depending on the models used.

Logic challenges

These results highlight logic challenges. Frail patients are not more likely to have certain frailty symptoms, but these symptoms are necessary to make these diagnoses. It is unclear whether the symptoms that frailty is insignificantly correlated with can be called "frailty" symptom or used for frailty diagnosis. When excluding these symptoms from being used for the diagnosis of frailty, the prevalence of frailty will likely decrease for the Functional Domain Model and the Biologic Syndrome Model and may increase or decrease for the Burden Model. Whether the updated indices will become insignificantly associated with other frailty symptoms is unclear. If the frailty symptoms that are not significantly associated with frailty should be excluded, many of the published frailty prevalence rates are likely to be overestimated or biased for the reason describe above. We have not identified any studies explicitly examine the significance of the associations between the frailty statuses and frailty symptoms they defined in their own models. We will continue exploring the causal relationship between frailty and frailty symptoms using other data sets in the future.

Limitations

This study has strengths in using a publicly accessible database that has been investigated in previous studies [1, 2]. The demographic characteristics reported in this study matched those

reported [1]. However, there are several limitations to this study. There are other statistical and epidemiological measures of association that can be tested to demonstrate the strengths of associations, including Chi-squared statistics and risk ratios [27, 28]. Odds ratios are adequate for cross-sectional studies to approximate risk ratios [17]. However, odds ratios can over- or under-estimate effect sizes if the underlying risk ratios are greater or less than 1, respectively [29]. Other measures of association will be explored in the future. Moreover, there are other factors influencing the correlations between frailty statuses and frailty symptoms, such as demographic characteristics. These factors can be adjusted using techniques, such as multiple regression [30, 31]. Lastly, this study used cross-sectional data and longitudinal follow-up of the strengths of the associations between frailty and frailty symptoms might help to answer important questions, such as whether the insignificant associations are transient, whether frailty predicts major outcomes better if insignificant frailty symptoms are discarded, and whether the biases induced by the frailty diagnostic criteria predict outcomes better than frailty symptoms. This will need to be explored in future research.

Conclusion

The frailty diagnoses defined by three models were assessed for their correlations with frailty symptoms of their own, those defined by the other two models, and bias variables using odds ratios and correlation coefficients. Frailty diagnoses lack significant correlations with some of their own frailty symptoms and some of the frailty symptoms defined by the other two models. This suggests that frail patients are not more likely to have certain frailty symptoms using any of the three frailty models. This finding raises questions like whether frailty symptoms lacking significant correlations with frailty statuses could be included to diagnose frailty and whether frailty exists and causes frailty symptoms. Further research to assess the causal relationships between frailty and frailty symptoms is needed and planned.

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References

1. Cigolle CT, Ofstedal MB, Tian Z, Blaum CS. Comparing models of frailty: the Health and Retirement Study. *J Am Geriatr Soc*. 2009; 57(5):830–839. https://doi.org/10.1111/j.1532-5415.2009.02225.x PMID: 19453306
2. Chao Y-S, Wu H-C, Wu C-J, Chen W-C. Index or illusion: The case of frailty indices in the Health and Retirement Study. *PLOS ONE*. 2018; 13(7):e0197859. https://doi.org/10.1371/journal.pone.0197859 PMID: 30020923
3. Chao Y-S, Wu C-J, Wu H-C, et al. Composite diagnostic criteria are problematic for linking potentially distinct populations: the case of frailty. *Scientific Reports*. 2020; 10(1):2601. https://doi.org/10.1038/s41598-020-58782-1 PMID: 32054866
4. Fried LP, Tangen CM, Walston J, et al. Frailty in Older Adults: Evidence for a Phenotype. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*. 2001; 56(3):M146–M157. https://doi.org/10.1093/gerona/56.3.m146 PMID: 11253156
5. St. John PD, Tyas SL, Montgomery PR. Depressive symptoms and frailty. *International journal of geriatric psychiatry*. 2013; 28(6):607–614. https://doi.org/10.1002/gps.3866 PMID: 22961757
6. Nascimento PPP, Batistoni SST, Neri AL. Frailty and depressive symptoms in older adults: data from the FIBRA study-UNICAMP. *Psicologia: Reflexão e Crítica*. 2016;29.
7. Uslu A, Canbolat O. Relationship Between Frailty and Fatigue in Older Cancer Patients. 2021.
8. Whitson HE, Cohen HJ, Schmader K, Morey MC, Kuchel G, Colon-Emeric C. Physical resilience: not simply the opposite of frailty. *Journal of the American Geriatrics Society*. 2018; 66(8):1459. https://doi.org/10.1111/jgs.15233 PMID: 29577234
9. Chao Y-S, Wu C-J, Lai Y-C, et al. Why mental illness diagnoses are wrong: A pilot study on the perspectives of the public. *Frontiers in Psychiatry*. 2022:614. https://doi.org/10.3389/fpsyt.2022.860487 PMID: 35573385
10. Hill AB. The environment and disease: association or causation?: Sage Publications; 1965.
11. Corporation RAND. RAND HRS Data Files, supported by NIA and SSA. *Data Products* 2016; http://www.rand.org/labor/aging/dataprod/hrs-data.html. Accessed Nov 29, 2016.
12. Health and Retirement Study, RAND HRS Data File (v.P) public use dataset. In: U01AG009740). PadbtUoMwfftNIoAgnN, ed. Ann Arbor, MI2016.
13. Strawbridge WJ, Shema SJ, Balfour JL, Higby HR, Kaplan GA. Antecedents of frailty over three decades in an older cohort. *J Gerontol B Psychol Sci Soc Sci*. 1998; 53(1):S9–16. https://doi.org/10.1093/geronb/53b.1.s9 PMID: 9469175
14. Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. *J Gerontol A Biol Sci Med Sci*. 2007; 62(7):738–743. https://doi.org/10.1093/gerona/62.7.738 PMID: 17634321
15. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *J Gerontol Biol Sci Med Sci*. 2007;62A.
16. Chao Y-S, Wu C-J, Wu H-C, et al. Using syndrome mining with the Health and Retirement Study to identify the deadliest and least deadly frailty syndromes. *Scientific reports*. 2020; 10(1):1–15.
17. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. New York, NY: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.
18. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatrics*. 2008; 8(1):24. https://doi.org/10.1186/1471-2318-8-24 PMID: 18826625
19. Belhekar VM. *Statistics for Psychology Using R*. SAGE Publications; 2016.
20. Schober P, Boer C, Schwarte LA. Correlation coefficients: appropriate use and interpretation. *Anesthesia & Analgesia*. 2018; 126(5):1763–1768. https://doi.org/10.1213/ANE.0000000000002864 PMID: 29481436
21. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal statistical society: series B (Methodological)*. 1995; 57(1):289–300.
22. *R: A language and environment for statistical computing* [computer program]. Vienna, Austria: R Foundation for Statistical Computing; 2016.
23. *RStudio: Integrated Development for R* [computer program]. Boston, MA: RStudio, Inc.; 2016.
24. Chao Y-S, Lin K-F, Wu C-J, et al. Simulation study to demonstrate biases created by diagnostic criteria of mental illnesses: major depressive episodes, dysthymia, and manic episodes. *BMJ Open*. 2020; 10(11):e037022. https://doi.org/10.1136/bmjopen-2020-037022 PMID: 33172939
25. Chao Y-S, Wu C-J. PP46 When Composite Measures Or Indices Fail: Data Processing Lessons. *International Journal of Technology Assessment in Health Care*. 2019; 34(S1):83–83.

26. She Q, Chen B, Liu W, Li M, Zhao W, Wu J. Frailty pathogenesis, assessment, and management in older adults with COVID-19. *Frontiers in Medicine*. 2021;8.

27. Argyrous G. Introduction to measures of association. *Statistics for Social Research: Springer*; 1997:313–318.

28. Khamis H. Measures of association: how to choose? *Journal of Diagnostic Medical Sonography*. 2008; 24(3):155–162.

29. Zhang J, Yu KF. What's the Relative Risk?A Method of Correcting the Odds Ratio in Cohort Studies of Common Outcomes. *JAMA*. 1998; 280(19):1690–1691. https://doi.org/10.1001/jama.280.19.1690 PMID: 9832001

30. Hastie T, Tibshirani R, Friedman J. *The Elements of Statistical Learning: Data Mining, Inference, and Prediction*, Second Edition. Springer New York; 2009.

31. James G, Witten D, Hastie T, Tibshirani R. *An Introduction to Statistical Learning: with Applications in R*. Springer New York; 2013.