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Measuring and Understanding the Health Impact of Greater Fatigability in Older Adults: A Call to Action and Opportunities

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Abstract

Different from fatigue, an instantaneous state of tiredness, weakness and lack of energy, fatigability is a trait that contextualizes whole-body fatigue to the level of activity (i.e., intensity and duration) with which the fatigue is associated. Fatigability can be perceived or performance-related. Measuring fatigability improves upon traditional fatigue measures by accounting for self-pacing as older adults likely slow down or limit their daily activity to maintain fatigue in a tolerable range. Anchoring fatigue to activities/tasks improves sensitivity and allows for meaningful comparisons across individuals/between studies, as well as evaluating change over time and treatment effects. Two well-validated approaches are utilized to measure perceived fatigability: 1) a 5-minute slow-paced (1.5 mph/0.67 m/s, 0% grade) treadmill walk immediately followed by Borg rating of perceived exertion; and 2) a self-administered 10-item questionnaire, Pittsburgh Fatigability Scale, with both physical and mental subscales. Many walking-based performance fatigability measures are based on certain lap time or distance, while the Pittsburgh Performance Fatigability Index uses raw accelerometry data to quantify percent of cadence decline over the entire long distance walking tasks. Perceived fatigability prevalence ranges from 20–90% in older adults varying by assessment tool, and is higher with advancing age and in women compared to men. Fatigability is associated with physical and cognitive function, fall risk, mobility decline, and mortality. Unfortunately, the available research lacks representativeness in terms of racial and ethnic diversity. The time is now to incorporate our established sensitive and validated fatigability measures into global research and clinical practice to better understand mechanistic underpinnings and reveal intervention effects to reduce the burden and lessen the consequences of greater fatigability worldwide.

Keywords

Fatigue; perceived fatigability; performance fatigability; physical performance; prevalence; outcomes

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Introduction

The construct of fatigability is a newcomer to the gerontology literature, becoming popularized following the endorsement as a research priority at the 2008 fifth *Bedside-to-Bench research conference, "Idiopathic Fatigue and Aging"* (1). Distinct from fatigue, an instantaneous state of tiredness, weakness and lack of energy (2), fatigability is a trait that contextualizes whole-body fatigue to the level of activity (i.e., intensity and duration) with which the fatigue is associated (1,2). Fatigability can be quantified as either perceived (i.e., how much an individual physically or mentally feels limited by their fatigue) or performance-related (i.e., how much an individual is slowed down by their fatigue) (3) (Figure 1). Whereas traditional global fatigue measures have been limited in their ability to detect expected associations with age and other clinical outcomes and interventions (4–6), measuring fatigability improves upon this because it accounts for self-pacing as older adults likely slow down or limit their daily activity to maintain fatigue in a tolerable range (2). Anchoring fatigue to activities/tasks improves sensitivity and allows for meaningful comparisons across individuals/between studies, as well as evaluating change over time and treatment effects (2,4–8).

Interestingly, the available literature suggests that perceived and performance fatigability identify different people (9–11), although one study of healthier older adults found a strong correlation (r=0.97) between perceived and performance fatigability (12). Furthermore, the multiple sclerosis (13–15) and rheumatoid arthritis literature (16) state that perceived and performance fatigability do not assess the same construct and recommend independent evaluation. Understanding perceived fatigability may help to better disentangle motivation or intention from physical capacity (15,17), whereas measuring performance fatigability can remove much of the subjectivity associated with self-perception and may help to better determine underlying pathophysiological mechanisms. Thus, perceived and performance fatigability are complimentary to each other and together could provide a more comprehensive and in-depth view of mobility and health in research and clinical practice settings.

Frequently Used Measures of Perceived and Performance Fatigability

In the aging literature, two well-validated instruments are most often used to measure perceived fatigability: 1) a 5-minute slow-paced (1.5 mph/0.67 m/s, 0% grade) treadmill walk immediately followed by Borg rating of perceived exertion (RPE fatigability; range 6–20) (9); and 2) a self-administered 10-item questionnaire, the Pittsburgh Fatigability Scale (PFS; range 0–50) (7).

RPE fatigability was initially developed to distinguish frail from non-frail individuals and purposefully designed to be low demand to minimize participant exclusion. RPE fatigability can be analyzed continuously, or using the cut point of RPE≥10 (i.e., more severe fatigability) corresponding to a perceived exertion as very light and above (9). Additionally, Simonsick et al. established RPE severity strata for categorical analyses (6–7, 8–9, 10–11 and ≥12) (18).

The PFS was developed as a low cost, participant-centered and self-administered measurement, the first to include fatigue and demand in a single instrument (7,19). The PFS has physical and mental fatigability subscales and asks individuals to report their expected or "imagined" fatigue levels (0 "no fatigue" to 5 "extreme fatigue") they would feel immediately after completing each of the ten activities that represent a range of intensity and duration, including physical, household, and social activities. Individual items are summed; subscale scores range from 0–50 (higher=greater fatigability). Cut points for more severe physical and mental fatigability are PFS Physical≥15 (7), and PFS Mental≥13 (19), respectively. Beyond binary classification, severity strata are also established for PFS Physical (0–4, 5–9, 10–14, 15–19, 20–24 and ≥25) and PFS Mental (0–3, 4–7, 8–12, 13–15, 16–19 and ≥20) to further understand gradient effects of perceived fatigability on health (20). A clinically meaningful change in PFS is 4 points (physical) and 3 points (mental) (21). Availability of the PFS in 18 languages facilitates worldwide use provides opportunities to understand global differences in perceived fatigability.

Several measures of performance fatigability are available, yet most relying on a similar computational approach: comparing an individual's gait speed at the beginning (or average speed) to their gait speed at the end of a walk (22). For example, Performance Deterioration is the percent of gait speed slowed between the 2nd and the next to last (9th) lap over a fast-paced 400-meter corridor walk (9). Higher performance fatigability is quantified as ≥6.5% slowed (9). A caveat with these performance fatigability measures is various types of walking tasks utilized (e.g., fast/usual-paced 400m walk, fast/usual-paced 6-min walk), resulting in different scales and distributions of performance fatigability scores, and making it difficult to compare across assessments (23). Moreover, older adults tend to have varied walking speed trajectories, making the assumption of linear and consistent speed decline invalid (23,24). To overcome these methodological issues, Qiao et al. recently developed the Pittsburgh Performance Fatigability Index (PPFI) that uses raw accelerometry data that can be applied to various long-distance walking tasks (e.g., fast/usual-paced 400m walk) (10). PPFI quantifies the percent of cadence decline during a walking task by comparing area under the observed individual cadence-versus-time trajectory to a hypothetical area that would be produced in the absence of fatigue (i.e., if participant sustained maximal cadence throughout entire walk). PPFI had stronger correlations against physical function than Performance Deterioration (10), indicating PPFI as a more sensitive performance fatigability measure, useful for early (i.e., subclinical) identification of people at risk of greater fatigability. Task-specific 3-level PPFI severity strata are established for usual-paced 400m walk (11). PPFI presents a new measurement opportunity for researchers and clinicians to compare performance fatigability from different walking tasks and track performance fatigability remotely and in real-world settings across cohorts and populations.

Prevalence of Greater Fatigability and Age/Sex Trends Among Older Adults

To date, 25 publications from 11 cohorts (5,7,9,17,18,20,21,25–42) have reported prevalence rates for perceived physical fatigability (Table 1); while 13 papers (17,19,21,30,34,38–41,43,44) include perceived mental fatigability (Table 2). Only 4 studies utilized performance fatigability measures, such as Performance Deterioration obtained from a fast-paced 400-meter walk (7,9) and mean gait change during a self-paced 6-minute walk

(45,46). Some additional studies included our fatigability measures of interest but were not included here due to small sample size (<50 participants) or unreported prevalence. Those studies recruited community-dwelling frail older adults from senior housing or hospitalized settings (47,48), individuals with depressive symptomatology (49) or obesity (50); patients with hip osteoarthritis (51), lung disease (52) or Charcot-Marie-Tooth disease (53); and hemiparetic stroke survivors (54) or breast cancer survivors (55). Yet, these studies rarely reported fatigability prevalence rates, raising the importance of studying and understanding fatigability in at-risk clinical populations.

Overall, the prevalence of greater fatigability was comparable using the same fatigability measures across cohorts for populations with similar age and health status. The majority of the published work came from three large prospective cohorts conducted mainly in the United States – the Baltimore Longitudinal Study of Aging (BLSA), the Long Life Family Study (LLFS), and the Osteoporotic Fractures in Men Study (MrOS). Among general community-dwelling older adults up to 100+ years old, the prevalence of greater perceived physical fatigability ranged between 20–30% for RPE fatigability, and 25–90% for PFS Physical (Table 1). Given the greater intensity of activities included in PFS compared to the slow walking task used in RPE fatigability, it is not surprising that reported prevalence of PFS Physical is almost doubled on average. Prevalence of greater perceived mental fatigability was around 20% for PFS Mental (Table 2). For populations with disability limitations (33), overweight/obese (36), or cognitive impairment (38), the prevalence of greater PFS Physical was reported to be higher, ranging between 60%-80%, signaling a higher burden of fatigability in these populations where interventions aimed to mitigate fatigability should be prioritized. Lastly, prevalence of greater performance fatigability is often not reported due to the lack of a binary cutoff point with existing measurements. Only in BLSA, the prevalence of greater performance fatigability was reported as ~20% as measured by performance deterioration. Thus, future epidemiologic studies are needed to establish prevalence rates of performance fatigability.

Furthermore, prevalence of greater perceived fatigability is higher with advanced age. Every 10 years older age relates to approximately 1.5 to 2-fold higher prevalence of greater perceived fatigability, regardless of assessment measure (Table 1). Additionally, evidence from LLFS and GRAS revealed that women had higher prevalence of greater perceived fatigability than men, with the differential widening from about 6% (60–69 years) to up to 25% (≥80 years) (5,37). Interestingly, only LLFS reported sex difference in perceived mental fatigability prevalence, with no differences except in the oldest age strata (90–108 years) where women reported about 4% higher rates than men (43). Limited available data on performance fatigability in older adults precludes our ability to comment on sex differences. Thus, research opportunities exist to further evaluate sex differences in performance fatigability among older adults.

Correlates and Consequences of Fatigability

Epidemiologic research in aging is in its early stages of understand the correlates and consequences of greater fatigability (Figure 2, Tables 1 and 2). Findings reveal that greater fatigability is associated with lower physical activity (25,36,40,56,57), worse cardiorespiratory fitness (11,39), constricted life-space mobility (17,39), worse sleep health (30), higher chronic inflammation (58,59), greater cardiovascular burden (27), frailty (12), worse mitochondrial energetics (31,60) and genomic markers (61), worse body composition (59), lower muscle mass (62), neural correlates (63), personality (32,44) and greater low back pain (42) (Figure 2). Most importantly, fatigability severity predicts functional limitations and mobility decline (18,21,26), cognitive function decline (64), falls (41), and mortality (20) (Figure 2).

There is a dearth of information on interventions aimed at mitigating fatigability. In a study of breast cancer survivors, after a 12-week exercise intervention of three individual fitness training sessions, participant's PFS Physical score decreased 4.4 points (~20% less reported fatigability from 63.6% to 45.5%) in the exercise group versus no change in control group (6). Future clinical trials are needed to identify optimal modality of exercise prescription to reduce fatigability among broader populations, including at-risk community-dwelling older adults and clinical populations, is warranted.

Gaps in Knowledge and Future Directions

Research regarding fatigability in older adults has rapidly accumulated over the past decade, however, the majority of data originates from three large U.S. prospective cohorts. Most studies recruited predominantly white, relatively healthy community-dwelling older adults, thus limiting the representativeness in terms of racial and ethnic diversity. Our review does revealed, however, a higher prevalence of perceived fatigability in other countries, such as Spain (33) and China (35), highlighting that the burden of perceived fatigability may differ by populations as their health and physical function may vary. Assessing fatigability globally is more feasible with access to validated questionnaires, such as the PFS, available in many languages, as well as the ability to integrate task-based performance measures. Thus, given the impact of greater fatigability on health, it is of urgent public health importance to understand the burden of fatigability in nationally representative samples that includes under-represented older adults in the United States and globally.

Individuals with greater fatigability tend to have poor cardiopulmonary function (65), which might further reduce their total physical activity levels (25) and higher disease burden (27), increasing their risk of mobility disability (18,57). Given that maintaining mobility is a hallmark for healthy aging, understanding mechanisms underlying fatigability severity and designing effective interventions to reduce fatigability are essential to prevent or slow down the disablement pathway in older adults. Without prospective longitudinal data, we are unable to establish causality to promote targeted lifestyle and/or pharmacological interventions. The Study of Muscle, Mobility and Aging, a newer longitudinal prospective cohort study of older adults includes measures of perceived and performance fatigability (11,66), thus providing new opportunities.

Measuring fatigability is critical in research settings and clinical practice because it provides a sensitive, person-centered holistic indicator of an individual's vulnerability to fatigue by capturing what an individual thinks they can do as well as how much effort it takes to perform standard activities. Given its high prevalence and being a prognostic indicator of deleterious aging, the time is now to incorporate these established sensitive and validated perceived and performance fatigability measures into research and clinical practice to better understand mechanistic underpinnings and reveal intervention effects to reduce the burden and lessen the consequences of greater fatigability worldwide.

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Biography

Nancy W. Glynn, PhD, FGSA, FACSM is an Associate Professor of Epidemiology and Director, Master's Degree Programs at the University of Pittsburgh, School of Public Health. She is a physical activity epidemiologist with advanced training in exercise physiology. Dr. Glynn's research focuses on novel methods to measure fatigability and physical activity in older adults to understand their role in the disablement pathway.

Yujia (Susanna) Qiao, PhD, ScM, received her PhD in Epidemiology from the University of Pittsburgh and Master in Science (ScM) from Johns Hopkins Bloomberg School of Public Health. She is trained as an epidemiologist and specializes in accelerometry, physical activity, physical function, and aging. Dr. Qiao's research interests center around wearable technology for human health and performance monitoring. Dr. Qiao is currently a Post-Doctoral Fellow at California Pacific Medical Center Research Institute in San Francisco, CA.

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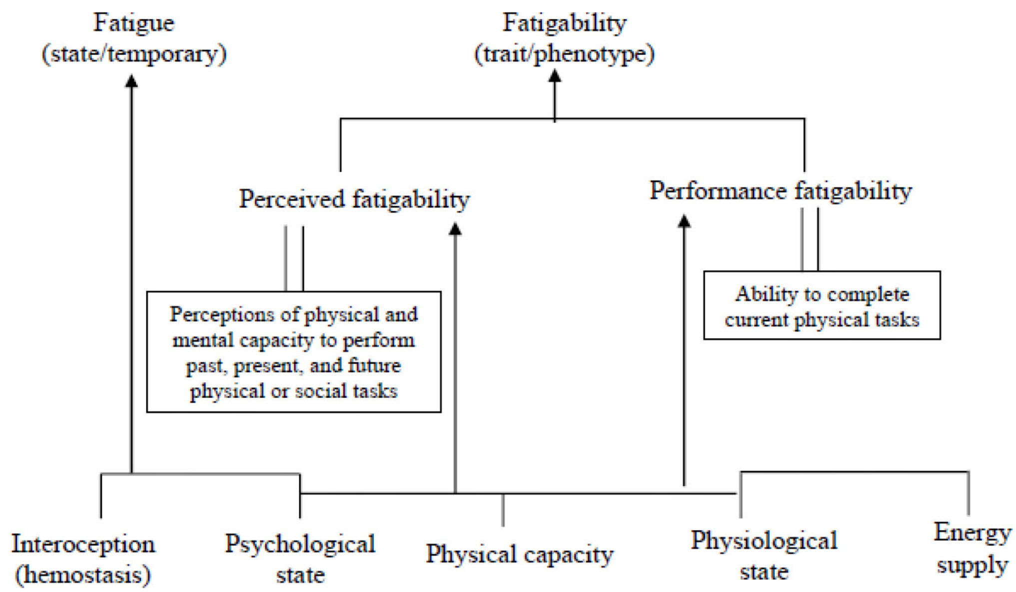

Figure 1.
Conceptual framework showing the characteristics of, as well as interdependent attributes that contribute to perceived and performance fatigability, adapted from Enoka 2021 (15)

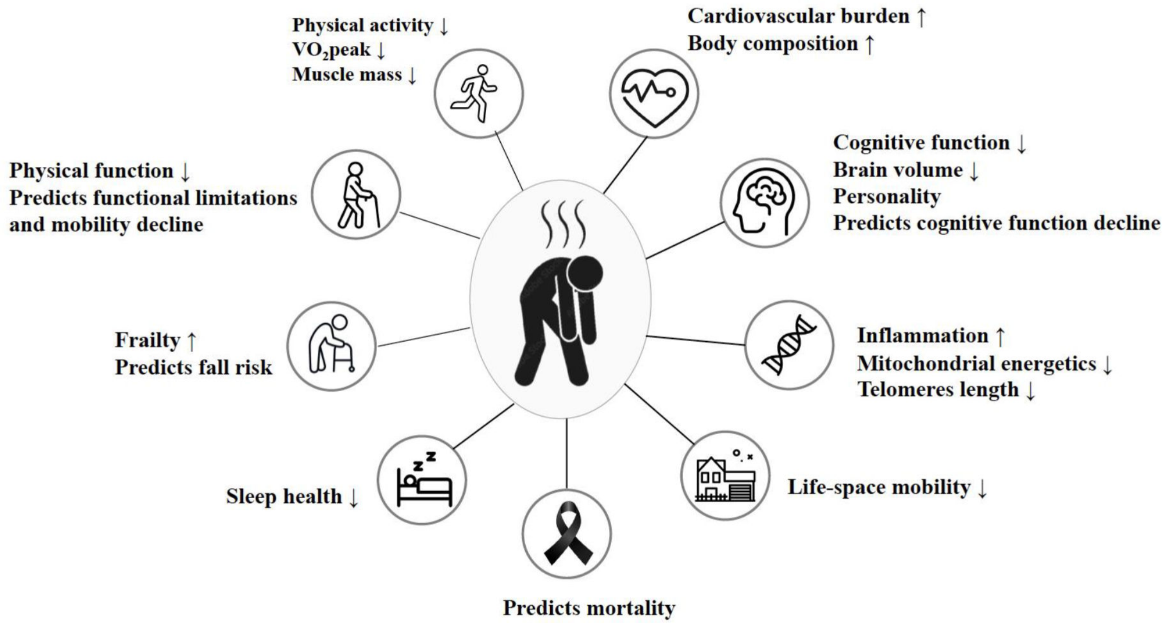

Figure 2.
Correlates and consequences of greater fatigability

Table 1.

Prevalence of greater physical fatigability among community-dwelling older adults (publications=25)

Study, Country	Publications	Sample Characteristics	How was fatigability measured?	Prevalence of Greater Physical Fatigability	Greater Fatigability Association with Health Outcomes
Baltimore Longitudinal Study of Aging (BLSA), USA	Glynn et al., 2015 (7); Simonsick et al., 2014 (9); Simonsick et al., 2016 (18); Simonsick et al., 2018 (21); Wanigatunga et al., 2018 (25); Gresham et al., 2018 (26); Qiao et al., 2019 (27); Martinez-Amezcua et al., 2019 (28); Simonsick et al., 2020 (29); Alfini et al., 2020 (30); Liu et al., 2021 (31); Chan et al., 2021 (32); Gonçalves et al., 2022 (42)	Sample size for perceived fatigability range: N=467–1665 Sample size for performance fatigability range: N=467–588 Age range: 65–97 yr Race/ethnicity: ~70% white	1) Borg Rating of Perceived Exertion (RPE) Scale (range 6–20) after 5-minute treadmill walk (1.5 mph at 0% grade) 2) Pittsburgh Fatigability Scale (PFS) Physical 3) Performance deterioration (PD): difference in lap times between the second and ninth laps during a fast-paced 400m walk (total 10 laps)	RPE fatigability: 20.0%-31.7% PFS: 41.1%-41.9% PD: 18.0%-22.8%	Cross-sectional findings: Gait speed ↓ Physical function ↓ Fitness ↓ Self-reported fatigue ↑ Walking ability ↓ Objective measured physical activity ↓ Physical performance ↓ Cardiovascular disease risk ↑ Adiposity ↑ Anemia ↑ Shorter total sleep time Wake bout length ↑ Mitochondrial function ↓ Personality Low back pain ↑ Longitudinal findings: Faster decline in physical function
Long Life Family Study (LLFS), USA and Denmark	LaSorda et al., 2020 (5); Glynn et al., 2021 (20)	Sample size range: N=2,258–2,355 Age: 73 ± 10 yr Range: 60–108 yrs Race/ethnicity: 99% white	PFS Physical	45.9% (16.2% most severe fatigability (PFS Physical ≥25)) By age strata: 60–69 yrs: 27.9% 70–79 yrs: 37.0% 80–89 yrs: 65.5% 90–108 yrs:89.5%	Cross-sectional findings: Body mass index ↑ Physical function ↓ Cognitive function ↓ Physical activity ↓ Longitudinal finding: Predicts mortality
Osteoporotic Fractures in Men Study (MrOS), USA	Moored et al., 2021 (17); Qiao et al., 2022 (40); Welburn et al., 2023 (41)	N=1113–1759 Age: 84 ± 4 yr Race/ethnicity: 91% white	PFS Physical	53.6%-56.0% (18.7% most severe fatigability)	Cross-sectional finding: Greater decline in physical activity Longitudinal finding: Predicts fall risk
Exercise Park Equipment for Improving Physical Function and Physical Activity Levels in the Elderly, Spain	Pérez et al., 2019 (33)	N=79 Age: 77 ±5 yr Race/ethnicity: not reported	PFS Physical	79.7%	Cross-sectional findings: Physical Performance ↓ Gait speed ↓ Self-reported weekly walking time ↓
Thyroid Hormone Therapy for Older Adults with Persistent	Stuber et al., 2020 (34)	N=276 (Placebo:134, Levothyroxine: 142)	PFS Physical	Baseline only: Placebo: 29.7% Levothyroxine: 46.2%	n/a

Study, Country	Publications	Sample Characteristics	How was fatigability measured?	Prevalence of Greater Physical Fatigability	Greater Fatigability Association with Health Outcomes
Subclinical Hypothyroidism (TRUST), Scotland, Ireland, the Netherlands, and Switzerland		Age: 74 ± 6 yr (placebo); 74 ± 5 yr (Levothyroxine) Race/ethnicity: 99% white			
Older adults, Mainland China	Hu et al., 2021 (35)	N=457 Age: 85 ± 6 yr Race/ethnicity: 100% Asian	PFS Physical	88.2%	Cross-sectional findings: Physical performance ↓ Activities of daily living ↓
Mobility and Vitality Lifestyle Program (MOVEUP) and Developmental Epidemiologic Cohort Study (DECOS) combined, USA	Graves et al., 2021 (36)	N=181 Age: 71 ± 7 yr Race/ethnicity: 74% white	PFS Physical	61.3%	Cross-sectional findings: Less Active/Robust and Later rest activity rhythms
Geisinger Rural Aging Study (GRAS), USA	Davis et al., 2021 (37)	N=122 Age range: 82–97 yr Race/ethnicity: predominately white (did not report exact number)	PFS Physical	Overall: 80.3% By age strata: 80–84 yrs: 38.8% 85–89 yrs: 41.8% 90+ yrs: 19.4%	Cross-sectional findings: Diet quality ↓ Physical function ↓
Keelung Community Study, Taiwan	Lin et al., 2021 (38)	N=114 Age: 67 ± 5 yr Race/ethnicity: 100% Asian	PFS Physical	60.0% By cognitive status: Cognitively normal: 39.6% Late-life depression: 80.0% Mild cognitive impairment: 57.5%	Cross-sectional findings: Physical function ↓
Study of Muscle, Mobility and Aging (SOMMA), USA	Moored et al. 2023 (39)	N=775 Age: 76 ± 5 yr Race/ethnicity: 86% white	1) RPE fatigability 2) PFS Physical	RPE fatigability: 19.0% PFS Physical: 53.0%	Cross-sectional findings: VO_2peak ↓ Life-space mobility ↓

Table 2.

Prevalence of greater mental fatigability among community-dwelling older adults (publications=11)

Study, country	Author, year of publication	Sample Characteristics	How fatigability was measured	Prevalence of Greater Mental Fatigability	Greater Fatigability Association Health Outcomes
Baltimore Longitudinal Study of Aging (BLSA), USA	Simonsick et al., 2018 (21); Alfini et al., 2020 (30); Renner et al., 2021 (19)	Sample size range: N=382–579 Age range: 60–89 yr Race/ethnicity: ~70% white	Pittsburgh Fatigability Scale (PFS) Mental	21.8%-28.9%	Cross-sectional findings: Gait speed ↓ Chair stand pace ↓ Self-reported walking ability ↓ Shorter and longer total sleep time Wake after sleep onset ↑ Trail Making Tests A and B ↑ Depressive symptoms ↑ Global fatigue ↑
Osteoporotic Fractures in Men Study (MrOS), USA	Moored et al., 2021 (17); Allen et al., 2022 (44); Qiao et al., 2022 (40); Welburn et al., 2023 (41)	N=1113–1759 Age: 84 ± 4 yr Race/ethnicity: 91% white	PFS Mental	22.2%-24.0%	Cross-sectional findings: Physical activity ↓ Personality (conscientiousness ↓, optimism ↓, and goal reengagement↓)
Two volunteer registries from University of Pittsburgh, USA	Renner et al., 2021 (19)	N=664 Age: 75 ± 6 yr Race/ethnicity: 96% white	PFS Mental	36.5%	Cross-sectional findings: Trail Making Tests A and B ↑ Depressive symptoms ↑ Global fatigue ↑
Long Life Family Study (LLFS), USA	Renner et al., 2021 (19); Cohen et al., 2021 (43)	Sample size range: N=1,917–2,361 Age: 73 ± 10 yr Race/ethnicity: 99% white	PFS Mental	Overall: 21.8–24.8% By age strata: 60–69 yrs: 14.5% 70–79 yrs: 18.6% 80–89 yrs: 41.5% 90+ yrs: 67.2%	Cross-sectional findings: Trail Making Tests A and B ↑ Depressive symptoms ↑ Global fatigue ↑
Thyroid Hormone Therapy for Older Adults with Persistent Subclinical Hypothyroidism (TRUST), Scotland, Ireland, the Netherlands, and Switzerland	Stuber et al., 2020 (34)	N=276 (Placebo:134, Levothyroxine: 142) Age: 74 ± 6 yr (placebo); 74 ± 5 yr (Levothyroxine) Race/ethnicity: 99% white	PFS Mental	Baseline only Placebo: 12.6% Levothyroxine: 22.7%	n/a
Keelung Community Study, Taiwan	Lin et al., 2021 (38)	N=114 Age: 67 ± 5 yr Race/ethnicity: 100% Asian	PFS Mental	66.7% By health status: Cognitively normal: 35.8% Late-life depression: 82.9%	Cross-sectional finding: Cognitive function ↓

Study, country	Author, year of publication	Sample Characteristics	How fatigability was measured	Prevalence of Greater Mental Fatigability	Greater Fatigability Association Health Outcomes
				Mild cognitive impairment: 61.5%	
Study of Muscle, Mobility and Aging (SOMMA), USA	Moored et al. 2023 (39)	N=775 Age: 76 ± 5 yr Race/ethnicity: 86% white	PFS Mental	22.0%	Cross-sectional findings: VO_2peak ↓ Life-space mobility ↓