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Self-Reported Fatigue and Its Cross-Sectional Associations with Physical Function throughout Adulthood: The INSPIRE-T Cohort

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Abstract

BACKGROUND: Fatigue negatively impacts health outcomes but its association with physical function across the adulthood remains unclear. **OBJECTIVES:** This study described self-reported fatigue levels across age and sex categories, investigated the associations between fatigue and physical functions, and examined whether age and sex moderated their associations.

DESIGN: Cross-sectional design.

SETTING: Community.

PARTICIPANTS: Nine hundred sixteen participants aged 20-100 years in the observational INSPIRE-T cohort study.

MEASUREMENTS: Participants were classified into four age categories. Fatigue was assessed using the Patient-Reported Outcomes Measurement Information System (Short Form v1.0 – Fatigue 8a) and physical function was assessed by handgrip strength (HGS, Kg), usual gait speed (UGS, m/s), both 5-repetition (5CR, s) and 30-sec chair rise tests (30sCR, times), isokinetic knee extension strength (IKES, N m), and maximum oxygen consumption ($\dot{V}O_2$ max, ml/kg/min). Multiple linear regressions were performed to examine the associations between fatigue and the physical function outcomes (all square-root-transformed). Interactions of fatigue with age and sex were considered. **RESULTS:** Fatigue levels were the highest in people 75+ years. Women had a higher fatigue level than men. Fatigue was significantly associated with decreasing performance in UGS, HGS, 5CR, and 30sCR but not in IKES and $\dot{V}O_2$ max. Interaction analyses revealed that fatigue was associated with reduced UGS as people age (Fatigue \times age: $B = -0.002$, 95% confidence interval = $-0.003, -0.001$). Sex did not moderate the association between fatigue and physical function.

CONCLUSIONS: Our study indicated that fatigue was negatively associated with several components of physical function. Although sex did not moderate the relationship between fatigue and physical function, the association between fatigue and low UGS was more pronounced with increasing age.

Key words: Aging, fatigue, gait speed, physical performance patient-reported outcomes.

Introduction

Fatigue is the persistent feeling of general tiredness and is a common subjective symptom in older adulthood (1). In a cohort of a nationally representative sample

of middle-aged and older adults living in US communities, the prevalence of fatigue was more than 30% (2), demonstrating an increasing age-related trend (3-5). Moreover, it has been shown that fatigue is frequently reported in primary care settings (6) and is more common and severe in women compared to men (1, 2, 7-9). Fatigue was also associated with adverse health-related outcomes, including physical functional decline, frailty, disability, disease risk, and mortality (5, 7, 10, 11). This imposes a significant medical and economic burden on individuals and society (12).

Physical function encompasses the capacity to perform basic and instrumental daily activities, and is measured by muscle strength, physical performance, and self-reported physical functioning (13). Studies on the association between fatigue and physical function in middle-aged and older adults have reported that higher perceived fatigue was strongly associated with reduced handgrip strength, lower limb power, and aerobic capacity (14, 15, 16). A systematic review suggested that fatigue-related physical decline might precede hospitalization, disease, and mortality (11). Yet, despite the importance of understanding the relationship between fatigue and physical function for early detection and interventions against functional decline, the relationship between fatigue and physical function and the potential moderating effect of age and sex on these associations remain poorly explored (4).

Regarding the moderating effect of age and sex, a study conducted in older adults indicated that perceived fatigue was prospectively associated with a greater likelihood of experiencing a clinically meaningful decline in usual gait speed in subjects aged 65-74 years but not in those aged 75-89 years (10). Another prospective study demonstrated that higher fatigue at baseline predicted a faster decline in gait speed at 5-year follow-up among men but not in women (17). Other studies reported no significant interaction effect between self-reported fatigue and sex on performance-based tests of physical functions (15, 16, 18). Thus, the interactions of fatigue with age and sex on physical functions are inconsistent across studies, partly because most of the studies were limited to older adults.

In fact, studies using objective measurements, such as knee extension muscle strength (19) and cardiopulmonary fitness (20), have demonstrated an age-related decline that initiates at

the age of 20. Therefore, a wider age range should be studied to observe the moderating effects of age and sex. As far as we know, no studies have examined whether the association between self-reported fatigue and objective performance measures of physical function varies according to age and sex across adulthood, including young, middle-aged, and older adults (11).

In this study, we aimed to: (1) describe the levels of perceived fatigue across a sample of individuals aged 20 years to more than 100 years; (2) investigate the associations of perceived fatigue with objective performance measures of physical function; and (3) examine whether such associations differed according to age and sex.

Methods

Study participants

This study used the baseline data of the INSPIRE Human Translational Cohort developed in Southwest, France. The details about the study design and data collection were published elsewhere (21, 22). Briefly, the INSPIRE Human Translational Cohort (INSPIRE-T) aimed to identify human biomarkers of healthy aging that could predict functional and resilience outcomes. This cohort is an observational study with a 10-year follow-up that started in October 2019 and included participants aged 20 and over (no upper limit for age). The recruitment process is stratified by 10-year age groups, with an oversampling of older individuals to investigate major clinical events. Given the heterogeneous nature of biological aging, we adopted flexible eligibility criteria from robustness to frailty, and even dependency. To monitor key risk factors for accelerated aging, we diversified recruitment sources, including media, online promotions, hospital outpatient clinics, general practitioners, residential homes, and nursing homes. Individuals with severe diseases compromising life expectancy to five years and those deprived of their liberty by administrative or judicial decision or under guardianship were not included. All participants provided their signed informed consent before entering the study. The INSPIRE-T protocol is available on <http://clinicaltrials.gov> (ID NCT04224038) and was validated by the French Ethical Committee located in Rennes (CPP Ouest V) in October 2019. The French “National Commission for Data Protection” provided its agreement on April 13, 2017 (Ref. Nb. MMS/OSS/NDT171027). The overall sample size of INSPIRE-T was 1014. The sample of present study was restricted to the participants with data on fatigue assessment (N = 916). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (23).

Fatigue assessment

Fatigue was assessed using the 8-item PROMIS-SF fatigue tool (24). The PROMIS-SF fatigue is a self-reported instrument that assesses and monitors perceived fatigue and the interference of fatigue in daily activities. All questions

assess fatigue over the past seven days. All items had response options on a 5-point Likert scale. Questions include: “How often did you feel tired?”, ranging from 1 (never) to 5 (always). The total raw score ranges from 8 to 40 and was converted into a standardized T-score with a mean of 50 and a standard deviation of 10. Higher scores indicated greater fatigue. T-scores were used for the analyses. The fatigue questionnaire was administered prior to physical function and cardiorespiratory fitness measurements.

Physical function assessments and cardiorespiratory fitness

Handgrip strength

The handgrip strength of the dominant hand was measured using a handheld dynamometer (JAMAR, Bolingbrook, IL, USA). Participants were asked to hold the dynamometer while standing with an angle of 90° between the arm and forearm, and to squeeze with their best effort. Each participant had three trials and the maximum value of all attempts was used in the analyses.

Usual gait speed

Usual gait speed was measured using the 4-meter gait speed test. Participants were instructed to start walking at a usual pace from a standing position behind the starting line to the finish line, which was four meters away (25). Each participant was timed for two attempts, and the faster walking was used.

Five-repetition chair rise test

In the five-repetition chair rise test, we asked participants to rise from the chair and to sit down five times as quickly as possible with their arms folded across their chest. The time from the initial sitting position to the final standing position (after the fifth stand) was recorded (25).

30-second chair stand test (30-s CST)

In the 30-s CST, participants were asked to complete sit-stand-sit cycles from a chair as many times as possible for 30 seconds. The total number of complete sit-stand-sit cycles was recorded (26).

Isokinetic muscle strength of knee extension

Isokinetic strength and VO₂ max were measured for a subsample only, on a voluntary basis. A Biodex System 3 dynamometer (Shirley, NY, USA) was used to measure the maximal isokinetic knee extension strength at an angular velocity of 60°/s. This isokinetic dynamometer is a reliable and valid instrument (27). The protocol started with a 5-min warm-up at 50-60 rpm on a cycle ergometer using a braking resistance corresponding to 2% of the subject’s body mass

(28). Participants were seated in the dynamometer adopting a standardized position of 85° hip flexion from the anatomical position. The lever arm was aligned with the lateral epicondyle of the knee. The range of motion was set at 85°, with knee flexion ranging from 5° to 90°. The initial 5° of flexion was completed. Concentric muscular contractions were then tested considering 5 repetitions for knee flexion and knee extension at 60°/s (1.05 rad/s). A 60-second interval was settled between the 3-repetition familiarization and the test. The maximum value of all attempts at both legs was recorded. Data were collected at a sampling rate of 100Hz and analyzed using Acqknowledge version 4.1 software (Biopac Systems, Inc., Goleta, CA, USA). To ensure reliable results, individual curves were carefully examined to identify true isokinetic torques within a 95% confidence interval of an angular velocity of 60°.s-1.

Maximum oxygen consumption ($\dot{V}O_2$ max)

Cardiorespiratory fitness was assessed through the measure of $\dot{V}O_2$ max on the same day one hour after the isokinetic muscle strength measurement. $\dot{V}O_2$ max was measured using a graded exercise testing protocol on an ergometer under medical supervision. The initial workload was set at 20% of the theoretical Maximal Aerobic Power (tMAP) derived from the Wasserman's prediction equation (29). This initial workload was sustained for 3 minutes. Then, the workload was increased by 10% of the theoretical power reserve ((tMAP-0.3tMAP)*0.10) every minute until exhaustion. We considered that the subjects achieved their $\dot{V}O_2$ max when all of the following criteria were met: maximal heart rate (HRmax) \geq 90% of the age-predicted at exhaustion, HRmax, respiratory exchange ratio \geq 1.10 at exhaustion, and not sustained a sufficient cycling rate.

Confounders

Based on the literature on both fatigue and physical function, we selected the following confounding variables: age, sex, education level, chronic conditions measured by a modified Charlson comorbidity index (CCI without dementia and metastatic solid tumor) (co-morbidity defined as CCI \geq 2; dichotomy) (30), activities of daily living (ADL) dependency assessed using the 6-item Katz scale (independent (ADL=6) or not, dichotomous) (31), instrumental ADL (IADL) assessed with the 5-item scale (independent or not, dichotomous) (32), cognition assessed with the Mini Mental State Examination (MMSE) (score range 0 – 30, higher is better) (33), body mass index (BMI) (kg/m², continuous) (34), and physical activity level evaluated using the International Physical Activity Questionnaire (IPAQ) long-form (MET-min/week, continuous) (35).

Statistical Analysis

Descriptive statistics (median and interquartile range (IQR), or frequencies and percentages) were used to characterize the study population as a whole, and according to age and sex categories and fatigue quartiles. Group differences for

continuous variables were examined using the Mann-Whitney U and Kruskal-Wallis tests, while categorical variables were tested using the chi-square test, as appropriate.

The associations between fatigue and the physical outcomes were explored through three consecutive steps. Firstly, multiple linear regressions were performed to examine the associations between each physical function, used as dependent variable, and fatigue, used as independent variable (Model 1). Secondly, we incorporated two interaction terms using age and sex with fatigue in order to test whether those factors could moderate the associations between fatigue and physical function (Model 2). In this respect, age was used either as categorical (model 2a) or ordinal (model 2b) variable composed of 4 groups (20-44, 45-64, 65-74, and \geq 75 years). The use of age as ordinal variable was performed to check whether the moderating effect of age followed a linear trend. Lastly, if any interaction term was significant, we performed stratified analyses in order to examine the relationship at each level of the identified moderator (model 3). All models were adjusted for the above mentioned confounders and those without ADL/IADL adjustments. Residuals' normality and homoscedasticity were verified for each regression model. Given that the residuals were skewed, all the outcomes and the measure of physical activity underwent a square root transformation. Significance level was set at 0.05. All statistical analyses were carried out using IBM SPSS Statistics Version 28 (Chicago, IL, USA).

Results

After removing the 98 individuals with missing data for PROMIS fatigue T-score, the present work included 916 participants (Table S1). The median age of the participants was 63.0 years (ranging from 20 to 100 years) and there were 62.7% of females. The mean and median PROMIS fatigue T-scores stood at 44.2 (Standard deviation: 9.1) and 41 (IQR: 33.1-50.4), respectively (Table 1). Notably, 27.9% of participants (n=256) reported not experiencing any fatigue, indicating a fatigue score of 8, while 27.3% of participants reported elevated fatigue levels with scores higher than 16 in raw score (50 in T-score) which are general US population mean.

Table S2 illustrates the participants' characteristics based on their fatigue quartiles. When comparing the lowest fatigue groups (Q1: median [IQR] = 33.1 [33.1-33.1]) with the highest fatigue group (Q4: 55.6[52.5, 59.4]), it appeared that the Q4 group comprised older individuals, a higher proportion of women, and subjects with lower educational attainment, as well as individuals with unfavorable physical conditions. In addition, the participants in Q4 exhibited significantly poorer performance in handgrip strength, usual gait speed, 5-repetition chair rise, 30-second chair rise, and isokinetic muscular strength compared to Q1. However, there were no significant differences between the groups with regard to $\dot{V}O_2$ max. Stratifying the sample according to age and sex categories, indicated that the 65-74 years age group (41.0 [33.1-48.1]) exhibited a significantly lower median fatigue score than the 20-44 years (44.3 [38.5-49.2]) and the 45-64 years (44.3 [33.1-49.2]) groups; while the median score of the 75+ years age group

Table 1. Participant characteristics in this study

Variables	Total	
	N	Median (IQR) or n (%)
Age, years	916	63.0 (48.6, 76.0)
Sex, women (%)	916	574 (62.7)
Education (%)	914	
Less than primary		3 (0.3)
Primary		36 (3.9)
Secondary		72 (7.9)
High school		125 (13.7)
Graduate or higher		678 (74.2)
Chronic conditions		
Charlson Comorbidity Index (2 or more) (%)	916	89 (9.7)
ADL status (less than 6 of ADL score) (%)	916	130 (14.2)
IADL status (less than 5 of IADL score) (%)	912	47 (5.2)
BMI, kg/m ²	916	24.6 (21.9, 27.4)
MMSE, points	916	29 (28, 30)
Physical activity, MET-min/week	848	1050 (442, 2079)
PROMIS-fatigue (T-score)	916	44.3 (33.1, 50.4)
Physical functions		
Handgrip strength, kg	914	32.0 (24, 40)
Gait speed, m/sec	904	1.3 (1.1, 1.4)
5-repetition chair rise, seconds	904	8.8 (7.0, 10)
30-second chair rise, times	676	15.0 (13, 18)
Isokinetic muscle strength, N/m	237	97.0 (69, 124.5)
V̇O ₂ max, ml/kg/min	231	23.0 (20, 31)

Values are median (IQR) or absolute numbers (%); Abbreviation: ADL, activities of daily living; IADL, instrumental activities of daily living; BMI, body mass index; MMSE, Mini-Mental State Examination; MET, metabolic equivalent task; PROMIS, Patient-Reported Outcome Measurement Information System; V̇O₂ max, maximal oxygen consumption. For continuous variables, medians were compared using Kruskal-Wallis test across all age groups and Mann-Whitney U test between each two groups of the four groups. Categorical variables were compared using the chi-square test.

(46.9 [38.5-54.1]) was significantly higher than the three other groups ($p < 0.01$). We also observed that women (45.6 [38.5-51.5]) had significantly higher fatigue scores than men (42.8 [33.1-49.2], $p < 0.001$). Further participants' characteristics are provided in Table S3 and S4.

Association between fatigue and physical functions

The results for Model 1 of the multiple linear regressions are presented in Table 2. Higher fatigue scores were significantly associated with reduced handgrip strength ($B = -0.008$; 95% confidence interval [CI] = -0.015, -0.001; $p = 0.029$), slower usual gait speed ($B = -0.003$; 95% CI = -0.004, -0.002; $p < 0.001$), and poorer performance in both the 5-repetition ($B = 0.009$; 95% CI = 0.005, 0.013; $p < 0.001$) and 30-second chair rise tests ($B = -0.011$; 95% CI = -0.017, -0.005; $p < 0.001$). No significant association was found between fatigue and isokinetic knee extension strength or V̇O₂ max. No significant differences in results were observed with or without ADL/IADL adjustments (Table S5).

Interaction of fatigue with age and sex

Models 2a and 2b from Table 2 presents the results of the interaction analyses and indicate that age significantly moderated the association between fatigue and usual gait speed. Using age as ordinal variable indicated a linear moderating effect of age such that the negative association between fatigue and usual gait speed was more pronounced with increasing age ($B = -0.002$; 95% CI = -0.003, -0.001; $p < .001$). Using age as categorical variable indicated that the effect of fatigue was significantly different in the 75+ years group compared to the 20-44 years group ($B = -0.005$, 95% CI = -0.008, -0.002; $p < 0.001$) (Figure 1). No further moderating effect of age was detected and no significant interaction between fatigue and sex was identified in relation to any of the physical functions. No significant differences in results were observed with or without ADL/IADL adjustments (Table S5).

Model 3 presents stratified analyses according to the age groups and revealed significant negative associations between fatigue and usual gait speed in both the 45-64 years ($B = -0.002$; 95% CI = -0.004, 0; $p = 0.035$) and the 75+ years

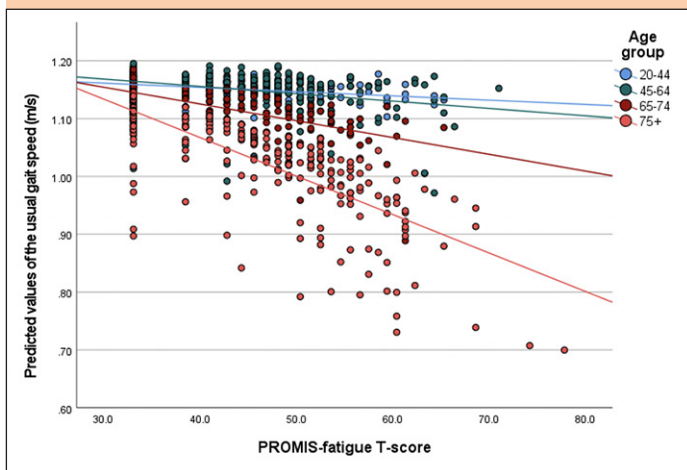
Table 2. Multiple linear regression models (with and without interaction between fatigue and age group or sex)

Independent variables	Handgrip strength	Usual gait speed	5-repetition chair rise	30-second chair rise	Knee extension muscle strength	V'O2 max
	n = 841	n = 840	n = 831	n = 660	n = 193	n = 191
Model 1						
fatigue	-0.008 (-0.015, -0.001)	-0.003 (-0.004, -0.002)	0.009 (0.005, 0.013)	-0.011 (-0.017, -0.005)	-0.005 (-0.013, 0.004)	0.001 (-0.013, 0.016)
Model 2a						
fatigue × age 75+	-0.001 (-0.021, 0.018)	-0.005 (-0.008, -0.002)	0.006 (-0.005, 0.018)	-0.001 (-0.018, 0.016)	-0.006 (-0.160, 0.149)	0.027 (-0.025, 0.080)
65-74	0.009 (-0.014, 0.032)	-0.003 (-0.006, 0.001)	-0.002 (-0.016, 0.012)	0.015 (-0.007, 0.036)	-0.020 (-0.159, 0.120)	0.018 (-0.028, 0.063)
45-64	-0.009 (-0.029, 0.010)	-0.001 (-0.004, 0.002)	-0.003 (-0.014, 0.009)	0.001 (-0.016, 0.018)	-0.001 (-0.135, 0.132)	0.010 (-0.034, 0.054)
fatigue × sex Women	0.003 (-0.010, 0.017)	-0.001 (-0.003, 0.001)	0.007 (-0.001, 0.015)	0.005 (-0.008, 0.017)	-0.061 (-0.157, 0.035)	0.001 (-0.031, 0.033)
Model 2b						
fatigue × age Age group (ordinal)	0.001 (-0.005, 0.007)	-0.002 (-0.003, -0.001)	0.003 (-0.001, 0.006)	0 (-0.005, 0.006)	-0.008 (-0.053, 0.037)	0.008 (-0.007, 0.023)
fatigue × sex Women	0.004 (-0.010, 0.018)	-0.001 (-0.003, 0.001)	0.006 (-0.002, 0.015)	0.005 (-0.007, 0.018)	-0.064 (-0.158, 0.029)	-0.001 (-0.032, 0.030)

Values are presented as coefficients (95% CI). Abbreviation: ADL, activities of daily living; IADL, instrumental activities of daily living; BMI, body mass index; MMSE, Mini-Mental State Examination; V'O2 max, maximal oxygen consumption. Model 1 was adjusted by age, sex, education, Charlson Comorbidity Index, ADL score, IADL score BMI, MMSE, physical activity, Model 2a was added interaction term of fatigue × age and fatigue × sex to Model 1, Model 2b was added interaction term of fatigue × age and fatigue × sex to Model 1 (age category was treated as ordinal scale). Bold p-values indicate statistically significant differences (p < 0.05)

groups (B = -0.005; 95% CI = -0.007, -0.002; p < 0.001). We also observed a negative trend within the older group aged 65-74 years (p = 0.078) (Table 3). The results for Model 3 are illustrated in Figure 1. Additionally, without adjustment for ADL and IADL, this association in the 65-74 years group was significant (B = -0.004; 95% CI = -0.006, -0.001; p = 0.016) (Table S6).

Figure 1. Cross-sectional associations between fatigue and usual gait speed (Model 2a)



The adjusted model considered covariates including age, sex, education, Charlson Comorbidity Index, ADL score, IADL score, BMI, MMSE, physical activity, the interaction term of fatigue × age, and fatigue × sex. ADL, activities of daily living; IADL, instrumental activities of daily living; BMI, body mass index; MMSE, Mini-Mental State Examination; PROMIS, Patient-Reported Outcome Measurement Information System.

Discussion

This study showed that self-reported fatigue levels were significantly higher in adults aged 75 years and older compared to the younger age categories, and were lower in older adults aged 65-74 years compared to young and middle-aged adults. Women had higher fatigue scores compared to men. Furthermore, higher fatigue scores were significantly associated with lower gait speed, handgrip strength, and chair rise performance while no relationships were found with isokinetic strength and V'O2 max. In addition, the association between fatigue and usual gait speed was moderated by age, with worse gait speed in people with fatigue 75 years or older; whereas no moderating effect of sex was detected.

Fatigue distribution according to age and sex categories

Interestingly, fatigue level was significantly lower in individuals aged 65-74 in comparison to young and middle-aged people, while it was sharply elevated in individuals aged over 75 years. A similar «J-shaped» relationship between fatigue prevalence and age have already been reported before (2), with several studies reporting the highest fatigue levels in adults aged 75+ (2-4, 36, 37) It has been proposed that fatigue reduces with age in healthy individuals but increases among those with chronic medical conditions (4, 36, 38, 39). Indeed, in our sample, the 75+ age group exhibited nearly three times the prevalence of multiple comorbidities compared to those aged 65-74. Furthermore, the low fatigue scores observed at ages

Table 3. Multiple linear regression models on the associations between fatigue and usual gait speed in each age group

Model 3							
Age group	N	B	SE	95% CI		p	R ²
20-44	183	-0.001	0.001	-0.003	0.001	0.357	-
45-64	268	-0.002	0.001	-0.004	0.00	0.035	0.061
65-74	158	-0.003	0.001	-0.005	0.00	0.078	0.181
75+	231	-0.005	0.001	-0.007	-0.002	<.001	0.545

Abbreviation: ADL, activities of daily living; IADL, instrumental activities of daily living; BMI, body mass index; MMSE, Mini-Mental State Examination; Adjusted Model was adjusted by sex, education, Charlson Comorbidity Index, ADL score, IADL score BMI, MMSE, and physical activity; Model 3 was adjusted by age, sex, education, Charlson Comorbidity Index, ADL score, IADL score BMI, MMSE, physical activity; Bold p-values indicate statistically significant differences ($p < 0.05$)

65-74 in our study could be partly explained by the positive “retirement effect”. Indeed, retirement was associated with a substantial decrease in both mental and physical fatigue in a large French cohort (40), and similar trends have been observed in the general US population (41). Besides being free from work stress due to retirement, retirement allows individuals to engage in more leisure physical and social activity, which may explain why they experienced less fatigue (40). Our data showed no significant difference in physical activity among subjects aged 65-74 compared to young and middle-aged groups. Based on these insights, it may be advisable to analyze fatigue levels separately for individuals aged 65-74 and those aged 75 and older, rather than grouping them together. If the J-shaped association of fatigue with age has any biological basis remains to be determined. However, it is plausible to hypothesize that higher levels of fatigue might be a marker of biological aging, since fatigue is associated with some important biological drivers of aging, such as mitochondrial energetics and function (42).

The finding of women experiencing higher levels of fatigue than men aligns with previous research (1, 2, 8, 9, 36, 43). Gender-specific biological and psychological factors could explain sex differences in fatigue. Women may experience fatigue due to menstruation, pregnancy, childbirth, and menopause. Additionally, psychiatric symptoms in women may be associated with increased fatigue levels (8). Moreover, in terms of cultural factors, the combination of employment with childcare and household responsibilities remains more burdensome for women than for men (9).

Association between fatigue and physical functions

To our knowledge, this study marks a pioneering effort in investigating the association between self-reported fatigue and objective physical functions across the whole adulthood. Our results showed a significant negative association between fatigue and various objectively measured physical functions, specifically usual gait speed, handgrip strength and chair rise test performance. These findings are in line with previous population-based studies indicating that self-reported fatigue levels were negatively associated with these physical functions in both middle-aged and older adults (15, 16, 44). This study is the first to investigate PROMIS fatigue and maximal tests such as isokinetic knee extension strength and $\dot{V}O_2$ max in healthy adults, finding no significant associations between

them. This lack of association requires exploration but may be due to the fact that the PROMIS tool does not assess acute physical fatigue following a maximum effort but rather evaluate perceived chronic fatigue including psychological fatigue (24, 45, 46). A previous study reported that, despite the negative impact of psychological fatigue on submaximal exercise, it appears that voluntary maximal strength and all-out cycling tests are unaffected (47). Moreover, another reason could be the small sample size. Additionally, the absence of association with isokinetic knee extension strength and $\dot{V}O_2$ max aligns with previous studies reporting no relationships between subjective fatigue and lower limb muscle strength in older adults (48); and no association between self-reported fatigue and $\dot{V}O_2$ max in various patient groups, including those with chronic fatigue syndrome (46). Although further research is needed to provide a comprehensive understanding of how fatigue associate with maximal and sub-maximal physical effort, our results consistently showed that high fatigue levels is associated with decreased physical performance regardless in both sexes and different age ranges.

Interaction of fatigue with age and sex and stratified analyses

We found that the negative association between fatigue and gait speed was more pronounced with increasing age, in particular in people 75+. Our findings extend the literature by including a wider age range of participants compared to previous studies reporting that the fatigue-low gait speed association was stronger in older adults compared to middle-aged adults (49) or younger older adults (44, 50). Our stratified analyses indicated that the associations between fatigue and gait speed becomes significant from middle age. Yet, it has been shown that people in their 40s who experience a reduction in gait speed are at higher risk for future health issues and are aging faster than their peers (51). This emphasizes the importance of detecting fatigue not only in older adults but also in middle-aged individuals. The lack of interaction regarding the other outcomes requires further investigations but may lie in the differing levels of effort required for each measurement. Usual gait speed does not require a maximal or even submaximal effort (since people are not requested to walk as fast as they can) whereas all other physical function measurements and cardiorespiratory fitness required (sub-) maximum effort, suggesting subjective fatigue could be

more sensitive to age when assessing usual rather than (sub-) maximum functional performance.

The lack of moderation effect of sex requires further exploration, including gender-specific biological factors, given the absence of prior studies in the literature. However, a large population-based cohort study revealed that the relationship between fatigue and physical function measurements, such as handgrip strength and chair rise test, were sex-independent (16), which supports our results. Thus, fatigue level could be negatively associated with handgrip strength and chair rise performance, regardless of age and sex.

Our study's strength lies in being the first to describe the fatigue distribution across a large age range representing the whole spectrum of the adulthood (from younger to very older adults) and to explore the associations between subjective fatigue levels and objectively measured physical function measurements and cardiorespiratory fitness. Moreover, we controlled for various potential variables that could affect the outcome. Furthermore, the novelty of our findings stems from uncovering the interaction between fatigue and age, highlighting the role of age as a moderating factor in the relationship between fatigue and gait speed. However, this study comes with certain limitations. Firstly, due to its cross-sectional design, establishing a causal relationship cannot be asserted. Secondly, the sample size was small for some outcomes such as isokinetic strength and $\dot{V}O_2$ max, because of the volunteer basis and the participant's safety. The small sample sizes might have limited the statistical power to detect associations. Moreover, INSPIRE is not a population-based, representative cohort; caution must be taken in generalizing of our findings to other populations because it did not include individuals with severe disease and those deprived of their liberty. Furthermore, the sample exhibited relatively lower fatigue than the general US population (T-score =50) (41). Furthermore, approximately 10% of the overall sample was excluded because of missing data on fatigue. Additionally, the sample size differences observed across the age groups might also have affected our analyses by assigning more statistical power to the larger groups. Finally, we lacked data on other potential contributors to fatigue such as anemia (52).

In conclusion, our study demonstrates that perceived fatigue was negatively associated with several components of physical function, including handgrip strength, gait speed, and chair rise test performance regardless of age and sex. Furthermore, it revealed that the associations between fatigue and usual gait speed were influenced by age, while sex did not have a moderating effect on the associations of fatigue with any of the physical outcomes. More research is needed to understand if self-reported fatigue is an early marker of future physical function/mobility decline during aging. Further work may also explore the biological mechanisms that underlie the relationships examined in this work, and longitudinal studies may help better understanding the role of fatigue in the life course trajectories of the physical functions. In the future, studies should consider investigating the associations between objective muscle fatigability and physical function.

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Ethical standards: The INSPIRE-T cohort is carried out in accordance with the declaration of Helsinki, which is the accepted basis for clinical study ethics and must be fully followed and respected by all engaged in research on human beings. The INSPIRE-T cohort protocol has been approved by the French Ethical Committee located in Rennes (CPP Ouest V) in October 2019. This research has been registered on the site <http://clinicaltrials.gov> (ID NCT04224038).

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