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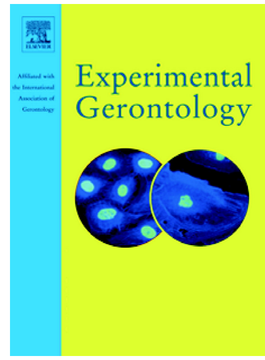

The interrelationship between grip work, self-perceived fatigue and pre-frailty in community-dwelling octogenarians

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Research Article

The interrelationship between Grip Work, self-perceived fatigue and pre-frailty in community-dwelling octogenarians.

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ABSTRACT

Introduction: Low Grip Work and high feelings of self-perceived fatigue could be an early characteristic of decline in reserve capacity, which comes to full expression as physical frailty in a later stage. When Grip Work and self-perceived fatigue can be identified as characteristics differentiating between robustness and pre-frailty it might allow to identify pre-frailty earlier. Therefore, this study aimed to investigate whether the combination of Grip

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Work and self-perceived fatigue is related to pre-frailty in well-functioning older adults aged 80 and over.

Methods: Four-hundred and five community-dwelling older adults aged 80 and over (214 robust and 191 pre-frail) were assessed for muscle endurance (Grip Work corrected for body weight (GW_bw)), self-perceived fatigue (MFI-20) and frailty state (Fried Frailty Index, FFI). A Capacity to Perceived Vitality ratio (CPV) was calculated by dividing GW_bw by the MFI-20 scores. ANCOVA analysis (corrected for age and gender) was used to compare robust and pre-frail older adults, and binary logistic regressions were applied to analyze the relationship between CPV and pre-frailty status.

Results: Pre-frail older adults who scored negative on the exhaustion item of the FFI still showed significantly lower GW ($p<0.001$), CPV ratios ($p<0.001$) and higher self-perceived fatigue ($p<0.05$) compared to the robust ones. The likelihood for pre-frailty related significantly to higher age, being men and lower CPV ratios. In women, every unit increase in CPV ratio decreased the likelihood for pre-frailty by 78% (OR 0.22; 95% CI: 0.11-0.44), for men this effect was less strong (34%, OR 0.66; 95% CI: 0.47-0.93).

Conclusions: Pre-frail community-dwelling persons aged 80 years and over without clinical signs of exhaustion on the FFI still experience significantly higher fatigue levels (lower Grip Work, higher self-perceived fatigue and lower CPV levels) compared to robust ones. CPV ratio could therefore be a good tool to identify subclinical fatigue in the context of physical (pre-)frailty.

HIGHLIGHTS:

- Non-exhausted pre-frail elderly report higher fatigue levels than non-frail ones
- Combined Grip Work and self-perceived fatigue predicts pre-frailty
- Capacity-to-Perceived Vitality ratio (CPV) captures early signs of fatigue

Keywords: Fatigue; Handgrip; Muscle Endurance; Pre-frailty; Community-dwelling; Aged; Vitality

1. INTRODUCTION

Frailty is a sign of losses in reserve capacity and can be conceptually defined as "*a clinical state in which there is an increase in an individual's vulnerability to develop negative health-related events (including disability, hospitalizations, institutionalizations, and death) when exposed to endogenous or exogenous stressors*" (Vella-azzopardi and others 2016). As a consequence, the frail person is at increased risk for different negative health outcomes such as disability, hospitalization and death (Vermeiren and others 2016). A widely accepted approach for the assessment of physical frailty consists of five components as described by

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Fried and others (2001): exhaustion, unintentional weight loss, low physical activity, slow walking and low grip strength. Fatigue, muscle atrophy (defined as sarcopenia) and muscle weakness are key elements in this phenotype. In the pathophysiology of frailty, sarcopenia, fatigue and inflammation have been recognized to play a predominant role (Bauer and Sieber 2008). Altogether, fatigue characterizes the depletion of physiological reserve capacity leading to a higher risk for negative health outcomes (Knoop and others 2021). However, it is unclear when fatigue plays a role in the development of frailty. Research on the occurrence of fatigue in the early stages of pre-frailty is crucial, as pre-frailty is believed to be reversible at this stage.

Generally speaking, fatigue can be divided into self-perceived feeling of fatigue and resistance to physical tiredness which includes a fatigue assessment such as muscle fatigability (Hardy and Studenski 2010; Knoop and others 2019; Zengarini and others 2015). A recent systematic review showed that fatigue has a prominent role in the operationalization of frailty and is included in most frailty scales (Knoop and others 2019). The different frailty instruments described in the literature cover a great diversity in fatigue constructs reflecting different underlying pathophysiological mechanisms by which fatigue relates to frailty. The fact that fatigue is a prominent element in the concept of frailty might be explained by the involvement of a chronic low-grade inflammatory profile (CLIP), considered as an important parameter in the pathogenesis of both fatigue and frailty (Hubbard and Woodhouse 2010; Krabbe and others 2004). Higher levels of circulating inflammatory markers such as C-reactive protein (CRP) are seen in older persons who are identified with physical frailty and sarcopenia (Marzetti and others 2019). Inflammation promotes sickness behaviour with fatigue as one of the symptoms (Dantzer and Kelley 2007) and is related to physical limitations and frailty (Cao Dinh and others 2019; Walston 2002).

Intrinsic capacity expresses all physical and mental capacities of an individual (Cesari and others 2018). Intrinsic capacity and frailty (Baerd JR 2019) are highly interrelated, in fact reduced intrinsic capacity is one of the factors leading to frailty. Where intrinsic capacity is more presenting the reserves of an individual, frailty focuses more on the deficit accumulation with ageing (Fried and others 2001). Grip Work and self-perceived fatigue provide complementary information in well-functioning older people (Bautmans and others 2010; Bautmans and others 2008), and could be parameters expressing the decline in intrinsic capacity. The oldest old, who are the most vulnerable, are the fastest growing group and have a higher risk for frailty. Therefore, there is an increasing need for a better understanding of

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the health and functional status of older persons and a need to prevent or at least delay the onset of late-life disability. Recent research has shown that fatigue is one of the early characteristics of frailty as signs of fatigue are already present approximately nine years prior to the occurrence of frailty (Stenholm and others 2019). However, it is unclear whether the combination of low Grip Work and high self-perceived fatigue reflects an increased risk for the loss of reserve capacity, which comes to full expression as physical pre-frailty. It is conceivable that good Grip Work and low self-perceived fatigue outweigh the deficits in reserve capacity, thus conserving the robust and independent state. It is clinically relevant to identify early predictors for physical (pre-)frailty to start interventions. Pre-frailty is a subclinical state of frailty but is only defined by certain frailty scales (Fried and others 2001; Kiely and others 2009). This shortcoming in frailty operationalisation points to the direct need for future research related to the identification of the early markers of frailty which constitute the pre-frail state. More detailed insight in the fatigue characteristics of pre-frailty in older adults can be useful for better understanding the possible pathways towards frailty. When Grip Work and self-perceived fatigue can be identified as characteristics differentiating between robustness and pre-frailty it might earlier identification of pre-frailty. Therefore, this study aimed to investigate if the combination of Grip Work and self-perceived fatigue is related to pre-frailty in well-functioning older adults aged 80 and over.

2. METHODOLOGY

2.1 Study design:

Baseline data were used from the BUTTERFLY study (BrUssels sTudy on The Early pRedictors of FrailtY), involving a cohort of community-dwelling older adults aged 80 and over, organized by the Vrije Universiteit Brussel (Belgium). The BUTTERFLY study aimed to identify early markers of frailty and healthy ageing in community-dwelling older adults aged 80 and over. This study was approved by the ethical committee of UZ Brussel (B.U.N. 143201421976), all participants signed informed consent.

2.3. Setting and participants

Four-hundred-ninety-four community-dwelling adults aged 80 years and over were recruited to participate in the BUTTERFLY study. The participants were recruited through advertisements via websites of the University Hospital in Jette in Belgium, general practitioners, pharmacies and health insurance companies. Participants were eligible for the study if they were aged 80 and over, could walk independently, lived independently, if they were mentally fit (MMSE>23/30), and not frail according to all three frailty instruments: the Groningen Frailty Indicator (GFI<4/15) (Steverink and others 2001), Rockwood Frailty

Index (RFI<0.25/10) (Collerton and others 2012), and/or the adapted Fried Frailty Index (FFI<3/4) (Sirola and others 2011); (exhaustion, weight loss, gait speed, and grip strength). Participants were excluded if they underwent surgery or any radiotherapy or chemotherapy during the past six months. Participants with CRP >10 mg/L were excluded, as this refers to an acute inflammatory state and not to a chronic low-grade inflammatory profile (Sproston and Ashworth 2018).

2.4. Measurements

2.4.1 Frailty score

As reported previously (Cao Dinh and others 2019), the adapted version of the physical phenotype of frailty in analogy to Sirola and others (2011) was used to determine frailty by a combination of 4 components: unintentional weight loss, exhaustion, weakness and low gait speed. Weight loss was evaluated by the self-reported question: “In the last six months, have you lost more than 4.5 kg unintentionally?” which was answered by yes (1) or no (0) (Fried and others 2001). Exhaustion was measured similarly to the original Fried phenotype, questioning two statements from the CES-D Depression Scale (Orme and others 1986): “I felt that everything I did was an effort” and “I could not get going”. The participants were asked: “How often in the last week did you feel this way?” and were scored (0) for rarely or none of the time, (1) for some or a little of the time, (2) for a moderate amount of time, or (3) for most of the time. When participants scored a 2 or 3 on either of the two statements, they received a point on the frailty scale for exhaustion. Gait speed was measured by timing the walked distance of 4.5 m and was stratified for gender and height, as proposed by Fried and others (2001). Participants were scored a point for slow walking if their walking time was ≥7 seconds in men ≤173 cm and women ≤159 cm, and if their time was ≥6 seconds in men >173 cm and women >159 cm. Grip strength was assessed using the Martin Vigorimeter; cut-offs were 42 kPa for women and 71 kPa for men (Cao Dinh and others 2019). Participants showing a grip strength below these cut-offs received a point for this item. In analogy to the original version (Fried and others 2001), the following scoring system was put forward to assign the level of frailty: a score of 0/4 signifies robustness, 1-2/4 points means pre-frailty, and with a score of 3 or 4/4 one is considered frail.

Maximal grip strength (Gsmax), fatigue resistance (FR), Grip Work (GW)

Participants performed a maximal handgrip strength (GSmax) and a Fatigue resistance (FR) performance test using a Martin Vigorimeter (KLS Martin Group, Tuttlingen Germany). The Martin Vigorimeter is a validated tool for measuring grip strength and muscle endurance in older adults (Bautmans and Mets 2005) and is provided with 3 different sizes of compressible rubber bulbs. For this study the large bulb was used as described previously (Bautmans and others 2007; Bautmans and Mets 2005). Briefly, the participants were asked to squeeze the bulb (with the dominant hand) three times as hard as possible, the highest score of the three attempts was registered as GSmax. After at least one minute rest, the FR was measured by asking the participants to squeeze in the bulb as hard as possible and to maintain this maximal effort as long as possible, under standardized verbal stimulation by the investigator. The time in seconds during which the GSmax dropped to 50% of its maximum was recorded as FR. These two parameters were used to calculate Grip Work (GW) by multiplying FR in seconds by 75% of the GSmax (GW= 0.75 * GSmax * FR) (Bautmans and others 2007). Grip Work represents the area under the time-strength curve, thus reflecting the physiologic work delivered by the muscles during the FR-test (Bautmans and others 2011) GW was also corrected for body mass (GW/body mass in kg) since overweight and obese participants will have to engage more strength and sustain that higher effort over time to execute their daily tasks (Bautmans and others 2011). Muscle endurance measures the ability to perform sustained maximal effort or for prolonged periods of time, which demands the physical capacity to resist muscle fatigue (Kent-Braun and others 2012; Theou and others 2008), and is significantly related to physical functioning in daily life (Bautmans and others 2008). Grip Work, a parameter reflecting the total effort produced during the fatigue resistance test was in this study used and reflects muscle endurance.

2.4.2 Self-perceived fatigue

The Multidimensional Fatigue Inventory (MFI-20) was used to assess the level of self-perceived fatigue. The MFI-20 is a self-reported fatigue questionnaire consisting of twenty items that cover five domains of fatigue: (1) general fatigue, (2) physical fatigue, (3) reduction in activity, (4) reduction in motivation, (5) cognitive fatigue (Smets and others 1995). If more than half of the items were missing, items were substituted by the mean of the non-missing items. Items are scored on a five-point Likert scale, a higher score (20-100) indicates higher fatigue and vice versa. In addition, the Mobility Tiredness scale (MOB-T) - designed to measure mobility-related fatigue in older adults – was used. It is questionnaire-based and counts the number of items where the participant reported tiredness after performing six activities; indoor transfers, walk indoors, go outdoors, walk outdoors in nice weather and walk outdoors in poor weather, and climb stairs. Low score refers to low fatigue and vice versa (Avlund and others 1993).

2.4.3 Inflammation & medical history

Non-fasting blood samples were taken by venepunction on the day of assessment, before

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performing the physical tests (body composition, muscle strength, endurance, fatigue and walking speed etc.). Circulating level of high sensitive C-reactive protein (hsCRP) was obtained by nephelometry (Behring, Marburg, Germany). When measurements of hsCRP fell below the LOD (Lower limits of detection <0.5 mg/L) (n=53), we imputed values from a uniform distribution between 0 and the LOD. The number of comorbidities derived from the Rockwood index (Collerton and others 2012) was collected based on the following list: hypertension, ischemic heart disease, cerebrovascular disease, peripheral vascular disease, heart failure, cancer within the previous 5 years, chronic lung disease, chronic joint disease, osteoporosis, diabetes mellitus, obesities thyroid disease, Parkinson's disease, dementia, eye disease, visual impairment, and hearing impairment. Data on the prevalence of high cholesterol (presence of dyslipidaemia), hypertension (based on a positive score on item 15 of the Rockwood index (Collerton and others 2012)), diabetes mellitus (DM) and use of statins was collected.

2.4.4 Anthropometry, body composition & Physical activity

Height and weight were measured (to the nearest exhaustio0.01m and 0.1kg respectively). Body fat was estimated using a fan beam whole-body DXA device (Hologic 4500 QDR upgraded to Discovery [Bedford, Massachusetts, USA]). Use of DXA to measure body composition is widely accepted and used in clinical practice (Smith-Ryan and others 2017; Vermeiren and others 2019). The Dutch version of the Yale Physical Activity Scale (YPAS) (Dipietro and others 1993) was used to measure the level of physical activity. This questionnaire is composed of two sections – 1) amount of physical activity/exercise performed during a typical week in the past month and 2) activities performed in the past month. The total energy expenditure summary index (kcal/wk) was calculated.

2.5. Statistical analysis.

Statistical analyses were performed using Statistical Package of the Social Sciences (SPSS) version 26 (IBM, Amonk, New York, USA) and the statistical software RStudio version 1.1.463 running on R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria). Significance was set a priori at two-sided $p < 0.05$. Average values are presented with mean ± standard deviation (SD) or median ± interquartile range (IQR, P75-P25) depending on measurement level and normality of distribution. Firstly, the prevalence of positive (combinations) frailty components of the FFI are presented as percentages (expressing the number of positive cases divided by the number of the total study population). Differences in age between robust and pre-frail older adults were investigated by the independent samples T-test, and a Chi-square test for ordinal variables. Next, differences between robust and pre-frail (divided into three pre-frail categories; (a) all pre-frail, (b) pre-frail older adults with and (c) without a positive score on the exhaustion item of the FFI) were explored by one-way Analysis of Covariance (ANCOVA) combined with a Bonferroni post-hoc test. Then the differences between robust and pre-frail older adults (divided into categories based on the positive items of the FFI: (a) pre-frail based on low grip strength, (b) pre-frail based on exhaustion, (c) pre-frail based on weight loss, (d) pre-frail based on slow walking speed) were explored by ANCOVA (supplementary table 1). Different combinations of frailty items were not included in the analysis to avoid losing statistical power caused by small number of participants in each subgroup. Next, an independent T-test was performed to investigate differences between men and women (supplementary table 2). We hypothesized that the relations between Grip Work, self-perceived fatigue and frailty status might be influenced by sex and age (Collard and others 2012), and thus we corrected for these variables. Next, partial Pearson correlations (corrected for age and sex) were computed to determine the association between frailty score and fatigue (GSmax, FR, GW corrected for body mass, self-perceived fatigue, CPV ratio and CRP). Then, binary logistic regression analysis using forward selection was conducted to assess whether the variables (age, BMI, CRP, body fat, GW and MFI-20 as independent factors) discriminated between robustness and pre-frailty, and odds ratios were calculated. Non-significant parameters were not used in the final models. The presented p values in table 4 are based on the Wald test. To test the hypothesis whether persons with low muscle fatigability and high feelings of self-perceived fatigue are more likely to be pre-frail, we investigated the interaction between muscle fatigability and self-perceived fatigue ($GW_{corrected\ for\ body\ weight}$* 1/MFI-20) on the occurrence of pre-frailty. Since a high score on the GW is considered to be good, as well as a low score on the MFI-20, a classic interaction computation as the product of these parameters would neutralize the linear increase in interaction score with combined worsening scores on muscle fatigability and self-perceived fatigue. Therefore, we recomputed the MFI-20 scores as 1/MFI-20 for testing its interaction with GW. All these interactions significantly predicted pre-frailty. To better interpret this interaction, a “Capacity to Perceived Vitality ratio” (CPV) was created in which “Capacity” refers to Grip Work and “Perceived” refers to self-perceived fatigue measured with the MFI-20. The CPV ratio was computed as $GW_{corrected\ for\ body\ weight}$ / MFI-20, resulting in high ‘combined’ fatigue levels when the ratio was low, and low ‘combined’ fatigue levels when the ratio is high. In total 5 different ratios were computed, CPV-total ($GW_{corrected\ for\ body\ weight}$ /MFI-20 total fatigue), CPV-general ($GW_{corrected\ for\ body\ weight}$

/MFI-20 general fatigue), CPV-physical ($GW_{corrected\ for\ body\ weight}$ /MFI-20 physical fatigue), CPV-redact ($GW_{corrected\ for\ body\ weight}$ /MFI-20 reduced activity), CPV-redmot ($GW_{corrected\ for\ body\ weight}$ /MFI-20 reduced motivation) and CPV-mental ($GW_{corrected\ for\ body\ weight}$ /MFI-20 mental fatigue), resulting in in high 'combined' fatigue levels when the ratio was low, and low 'combined' fatigue levels when the ratio is high. Since the exhaustion component is part of the frailty index, we performed the same analysis on a subgroup, in which persons who scored positive on the CES-D item of the frailty index were excluded. Thus, model 1 includes all participants and model 2 excluded participants who scored positive on exhaustion (FFI). To avoid multicollinearity problems (r>0.80) we have implemented the CPV ratio's in independent regression models. To have a clear visualisation of the independent variables and their relation with pre-frailty, different effect plots were generated. Since we found an interaction between CPV ratios and gender (supplementary table 2), we performed separate logistic regression analyses for men and women for a better clinical interpretation of the results. Lastly, ROC curves were plotted to evaluate and visualize the fit of the logistic regression in distinguishing between robustness and pre-frailty.

3. RESULTS

This study included 405 participants (mean age 83.1±3.2 years, range 80 – 97 years, flowchart shown in Fig. 1) among which 214 robust (91 men and 123 women) and 191 pre-frail (136 men and 55 women) older adults. Pre-frail participants were significantly older than their robust counterparts (respectively 83.8±3.2 and 82.3±2.1 years, p<0.001). Low grip strength is the most prevalent positive frailty criterion in the pre-frail older adults, followed by exhaustion and low gait speed (see table 1.). Twenty-five participants scored positive on more than one frailty criterion, of whom 14 on exhaustion combined with low grip strength (see table 1).

The participants' characteristics are shown in table 2. Missing data was completely at random, there was no relationship between the missingness of the data and any values, observed or missing. No differences regarding DM, hypertension, high cholesterol, statins use, and number of comorbidities between robust and pre-frail older adults was found. Robust participants had significantly higher GW (p<0.001), less fatigue on the MOB-T (p<0.05) and MFI-20 (total, general, physical) (p<0.05) and better CPV ratios (p<0.001). Pre-frail older adults without the participants who scored positive on the exhaustion item of the FFI index still showed lower levels of GW (p<0.001) and CPV ratios (p<0.001), and higher levels on the MFI-20-total (p<0.05) compared to their robust counterparts. When looking at

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pre-frail adults who scored positive on the exhaustion item of the FFI, it can be seen that they scored lower on Grip Work and CPV levels and higher on CRP compared to robust participants, and higher levels for self-perceived fatigue (except of MFI-20 mental fatigue) were shown compared to robust and all other pre-frail participants (all pre-frail and pre-frail without the persons who scored positive on the exhaustion item). In the pre-frail participants, men show higher levels of Grip Work and higher CPV ratios compared to women, while women were more fatigued on the MOB-T (supplementary table 2)

Table 3 shows a negative relationship between GW and the FFI, in the participants who scored negatively on exhaustion, considering that better GW was related to a lower score on the FFI. No significant relations between MFI-20 and the FFI score were found in this group. All CPV ratios were negatively related to the FFI, considering that lower ratios are related to a higher score on the FFI. Considering all participants, positive relationships between MFI-20, MOB-T and frailty were found, indicating that higher levels of fatigue based on the MFI-20 (total and subscales) and MOB-T scores were related to a higher score on the FFI. In contrast, lower CPV ratios were significantly related to higher FFI scores.

A binary logistic regression was performed per CPV ratio (sub)scale with pre-frailty as dependent variable (table 4 and supplementary table 2). The regression analyses indicated that in all models age and the interaction between sex and CPV ratios were significantly associated with pre-frailty. CRP, physical activity and percentage body fat, did not significantly contribute and thus were not retained in the final models. The likelihood for being pre-frail increases with age and decreases with a higher CPV ratio. A significant interaction between CPV ratios and sex was found (supplementary table 3). Figure 2 shows this interaction and indicates that with increasing CPV ratio, the likelihood for pre-frailty decreases more for women compared to men. For a better clinical interpretation of this interaction, we performed the same analyses for men and women separately (table 4). In our study, men are more likely to be pre-frail compared to women. With increasing CVP ratio, the likelihood for pre-frailty decreases significantly. These results were found for all CPV ratios and the visualisations of these effects are shown in supplementary Figures 1a-2f. A separate logistic regression was performed per gender; in women every unit increase in fatigue ratio showed to decrease the likelihood for pre-frailty with 77.6% (CPV total model 1 OR 0.224; 95% CI: 0.114-0.440). In men these results were also present but less strong as for women (34,4%; CPV total model 1 OR 0.656; 95% CI: 0.465-0.926). The odds ratio for the total group using the CPV-total scale was slightly higher when excluding persons who scored negative on the CES-D item for men (model 1 OR 0.656; 95% CI: 0.465-0.926: model 2 OR

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0.711; 95% CI: 0.501-1.008), for women we found the opposite (model 1 OR 0.224; 95% CI: 0.114-0.440: model 2 OR 0.173; 95% CI: 0.076-0.391). ROC curves were plotted in order to evaluate and visualize the fit of the logistic regression for all total models (supplementary Figures 3a- 3L). The highest AUC was observed for CPV-physical ratio (AUC: 0.782, see supplementary table 3).

4. **DISCUSSION**

In this study, we investigated whether the combination of Grip Work and self-perceived fatigue is related to frailty in well-functioning older adults aged 80 and over. The main finding of this study was that also in participants who are pre-frail but did not show clinical signs of fatigue on the exhaustion component in the FFI, still experienced significantly higher fatigue levels (lower Grip Work, higher self-perceived fatigue and lower CPV levels) compared to their robust counterparts. Pre-frail participants who did score positive on the exhaustion item showed significant higher inflammatory levels compared to other pre-frail and their robust counterparts. However, CRP did not significantly contribute to the likelihood for pre-frailty and thus were not retained in the final regression models. Logistic regression analysis showed that age, gender, CPV ratio and the interaction between CPV ratio and gender were significantly associated with pre-frailty, in community dwelling octogenarians, with overall predictive accuracy of 77%. As a significant interaction was found between muscle fatigue and self-perceived fatigue, we computed a CPV ratio since this value is clinically more informative to interpret than the statistical interaction. Women were less likely to be pre-frail and with increasing CVP ratio the likelihood for pre-frailty decreased significantly, for men this effect was also found but less strong. Grip Work correlated significantly but moderately with self-perceived fatigue, suggesting that both provide complementary information regarding the clinical expression of fatigue. It cannot be excluded that self-perceived fatigue is related to aerobic capacity (cardiorespiratory plus muscular plus osteoarticular systems) however we expect that when there is a combination of low Grip Work and high self-perceived fatigue the same underlying mechanisms are involved. Therefore, the interplay between these two variables expressed as the CPV ratio might be a good fatigue "index" in frailty assessment to detect pre-frailty earlier. All CPV ratios showed a stronger relationship with the FFI than Grip Work and self-perceived fatigue separately; and logistic regression showed that CPV ratio can discriminate between robust and pre-frailty status. Results showed that age and the CPV ratio were significantly associated to the frailty status, even when the pre-frail participants did not score positively on the fatigue item in the FFI.

In this study we found a negative relationship between Grip Work and frailty, indicating that low Grip Work is related to a higher score on the FFI. This is in line with earlier research where it was shown that muscle fatigue and frailty share the same biomedical determinants (i.e. aging, disease, inflammation, physical inactivity, malnutrition, hormonal deficiencies, subjective fatigue and neuromuscular function and structure) (Theou and others 2008). The group of Westerblad showed that muscle endurance decreases before the onset of muscle weakness in a mouse model of premature aging (Yamada and others 2012). This is induced by defective proofreading function of mitochondrial DNA polymerase, mitochondrial function translates into physical function and behaviour, suggesting that the amount of energy the cells can produce will determine the total energy sum, which an individual can use in daily functioning (Kent and Fitzgerald 2016). This supports the hypothesis that Grip Work might be a good early marker for frailty (Kent-Braun and others 2002) and therefore potentially highly relevant in identifying individuals who are progressing towards frailty. Thereby, it has been shown that Grip Work can help to discriminate older women with different degrees of frailty (De Dobbeleer and others 2018). Interestingly, we found significant differences in self-perceived fatigue and Grip Work between robust and pre-frail participants, also within participants who scored negatively for the exhaustion item in the FFI. This could imply that persons who do not score positively on exhaustion in the FFI show already early signs of fatigue. However, this was not detected by the CES-D questions, one of the key elements in the FFI (Orme and others 1986). The CES-D items in the FFI were included by Fried and others (2001) assuming that they indicate exhaustion, comprising low energy and poor endurance. Depending on how the symptom is referred, several terms are interchangeably used to define fatigue, such as tiredness, exhaustion, fatigability, low vitality, anergia, in fact the definition of fatigue is still largely debated (Zengarini and others 2015). Previous research showed that fatigue in frailty operationalization has a large heterogeneity since it was defined in 32 unique ways. Furthermore, exhaustion as described in the FFI belonged to the concept of self-perceived fatigue according to the framework proposed by Knoop and others (2019). These CES-D items are associated with the VO2max and are able to predict cardiovascular disease (Fried and others 2001). Multiple adapted FFI versions used other fatigue instruments to capture the exhaustion item including generic questions such as feeling tired or feeling worn out, and questions from the 36-item Short Form Health questionnaire (Knoop and others 2019). Despite the large array of operationalization, all exhaustion items belong to the same ICF category (Azzopardi and others 2016). However, it is questionable if these tools are capable to detect early stages of fatigue. In our study, we

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found that participants show already signs of losses in reserve capacity expressed by a low CPV ratio before they score positive on the CES-D exhaustion items. Therefore, it can be hypothesized that including a measurement of Grip Work in combination with self-perceived fatigue can be a valuable asset in early physical frailty identification. This will help developing preventive and therapeutic interventions.

In contrast to other studies (Cao Dinh and others 2019; Walston 2002), we did not find a significant relationship between inflammation and frailty status. In addition, no significant relationship was found between CRP and Grip Work. These results are contradictory to other articles that showed a relationship with inflammation in community-dwelling older persons (Bautmans and others 2007; Beyer and others 2012a) and in hospitalized geriatric patients (Arnold and others 2017; Beyer and others 2012b). However, literature in healthy community-dwelling older adults is scarcer, which could explain the lack of similar findings. In our study, we included relatively high performing non-frail participants (i.e. independent living in the community, physically active (high scores on the YPAS), no major medical health conditions and physiological fit (MMSE >23)) who were not frail and who performed sufficient physical activity, which might decrease the risk for inflammaging. As CRP was used to exclude participants with ongoing inflammatory pathology; not primarily to quantify low-grade inflammation. Therefore, we might have missed the influence of low-grade inflammation in our statistical analysis. Also, other inflammation markers such as (IL-6, TNF-α, IL-1β …), which are also elevated with ageing (Krabbe and others 2004) could be included to investigate the role of inflammation in the risk for pre-frailty. Since older adults showing higher inflammatory markers are more prone to frailty (Cao Dinh and others 2019; Soysal and others 2016).

We hypothesized that fatigue is a valid parameter for intrinsic capacity, a concept introduced by the World Health Organization (WHO). Recently 5 domains have been selected that cover the construct of IC of which: locomotion, vitality, sensory, cognition and psychological (Cesari and others 2018). Reduced intrinsic capacity will have implications on the level of physical functioning. The WHO suggests that changes in intrinsic capacity are likely to start at midlife, before persons will experience problems in daily functioning. It is hypothesized that some parameters will influence the depletion of reserve capacity leading to enlarged risk for frailty. The combination of high self-perceived fatigue and low Grip Work could be recognized as deficits modifying intrinsic capacity and partly determine the development of frailty. There is growing interest in the vitality domain of IC, being considered as a condition for proper IC rather than as a separate domain. Vitality describes the variance in complex and biologic systems which sustain life and functioning(Cesari and others 2018). However, there is no consensus regarding the clinical evaluation of vitality. Low Grip Work when combined with high self-perceived fatigue might be a good asset for evaluating intrinsic capacity and increase the clinical usage of the vitality domain. However, the exact role of these two parameters in this concept has not been investigated before and should be validated. The results of this study show that muscle fatigue and self-perceived fatigue are a good indicator for early stages of pre-frailty. Men were more likely to be pre-frail in this cohort, especially those with a low CPV ratio. This is in contrast with earlier research where women were more likely to be pre-frail (Collard and others 2012; Gordon and others 2017). However, this is the first report on persons aged 80 and over. Since in our sample there were more men than women, this could have influenced the results. Women with better CPV ratios are less likely to be pre-frail; in men the same results were found but the effects were less strong. This suggests that the level of fatigue might be more important for women in the pathophysiology for frailty, considering that other characteristics are involved in men and women.

As far as we know, this is the first study suggesting that the CPV ratio could be an additional characteristic in the early identification of physical frailty. However, our study is based on cross-sectional data, and the results should be confirmed prospectively. The ROC curves found in this study show acceptable to good AUC value (range 0.755 – 0.782)(Mandrekar 2010), suggesting a decent prediction of pe-frailty. However, this study did not aim to provide diagnostic accuracy regarding the logistic regression analyses and neither to compare the CPV ratio against the FFI as a "gold standard" for frailty. The reported ROC curves aim to report on the strength of the logistic regression analyses that were performed, to give more insight in the characteristics of fatigue in pre-frail participants. A longitudinal approach may allow developing cut-off values for the CPV ratio for the identification of pre-frailty. For clinical practice, the results showed that robust older adults showed on average a CPV total score >1, while pre-frail older adults had on average a score <1. Every unit increase of CPV score decreased the likelihood for pre-frailty with 34% for men and 78% for women. Since pre-frail men showed to have better Grip Work and better CPV ratios (supplementary table 2) compared to pre-frail women, it is possible that every unit increase in CPV score has in proportion a smaller effect for men than for women. This might be the explanation why every unit increase of CPV score differs between men and women, however this should be validated in a longitudinal approach.

This study has certain strengths and limitations. The strength of this study relies in the inclusion of a relatively large and unique cohort considering the age and independence level

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of the participants, providing unique data on potentially early determinants of frailty. The participants were robust older adults 80 years and over with no major medical health conditions. No significant differences regarding medical conditions between robust and pre-frail older adults were found, therefore we do not expect this influenced the association between pre-frailty and fatigue. It cannot be excluded that the lack of statistical differences and relationships between frailty status and inflammation is due to the fact that on the one hand we recruited participants without ongoing inflammatory pathology, and on the other hand that the CRP-assay lacked sensitivity. The finding that men were more likely to be pre-frail might be due to an uneven distribution of men and women in our study sample. Most literature refers to women as the risk group for developing frailty but woman are also likely to be frail at a younger age compared to men (Gordon and others 2017). Since we included persons aged 80 and over, it could be that we excluded the frail women and were left with a higher prevalence of pre-frailty in men. However, the CPV ratio was significantly related to pre-frailty for men and women when analysing separately. This study used the adapted version of the FFI and left out the physical activity component. This approach could have underestimated the prevalence of pre-frailty, however research showed that low physical activity was one of the last items on which participants score positive in the frailty index (Stenholm and others 2019). Therefore, we expect no influence of this approach on the results. The total accuracy rate of the models leaves room for improvement and implies that other variables should be included in the early detection of physical frailty. However, we have included percentage body fat, physical activity and inflammation, but these parameters did not contribute significantly. On the other hand, it might be possible that the CPV captures a phenotype that is not completely detected by the FFI. Finally, all findings in this study are based on a cross-sectional analysis, and prospective confirmation is advocated, as pre-frailty is an unstable condition and reverse causation cannot be excluded.

5. CONCLUSION

Our study showed that older pre-frail persons without clinical signs of exhaustion experience significantly higher fatigue levels (i.e. lower Grip Work, higher self-perceived fatigue and lower CPV levels) compared to their robust counterparts. The “Capacity to Perceived Vitality” (CPV) ratio, representing the ratio between Grip Work and self-perceived fatigue, can be considered as a good candidate as early marker of (pre-) frailty. For clinical practice, every unit increase CPV ratio decreased the likelihood for pre-frailty with 34% for men and 78% for women. CPV ratio could therefore be a good tool to identify subclinical fatigue in the context of physical (pre-)frailty.

Statements

Acknowledgement

N/A

Statements of ethics

All participants gave their written informed consent and the study protocol was approved by ethical committee of the Universitair Ziekenhuis Brussel (B.U.N. 143201421976).

Conflict of interest

The authors have no relevant conflicts of interest to declare.

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Author Contributions

V.K. contribute to the data collection, data analysis, and writing of the manuscript. **A.C., A.D., R.V.A.** and **S.V.** contribute to data collection and reviewed the manuscript. **S.v.L.** contribute to the statistical analyses. **A.S.** and **B.J.** contribute to supervision and reviewed the manuscript. **I.B.** conceived the study, was responsible for funding acquisition, supervision, reviewing and editing of the manuscript. On behalf of the **Gerontopole Brussels Study Group**

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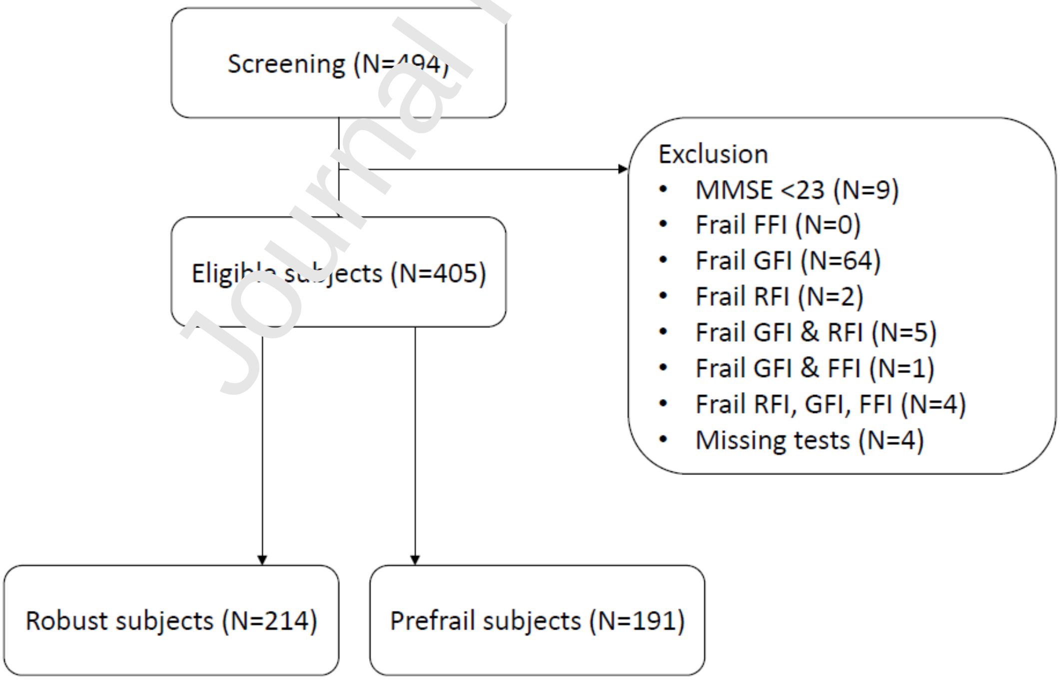
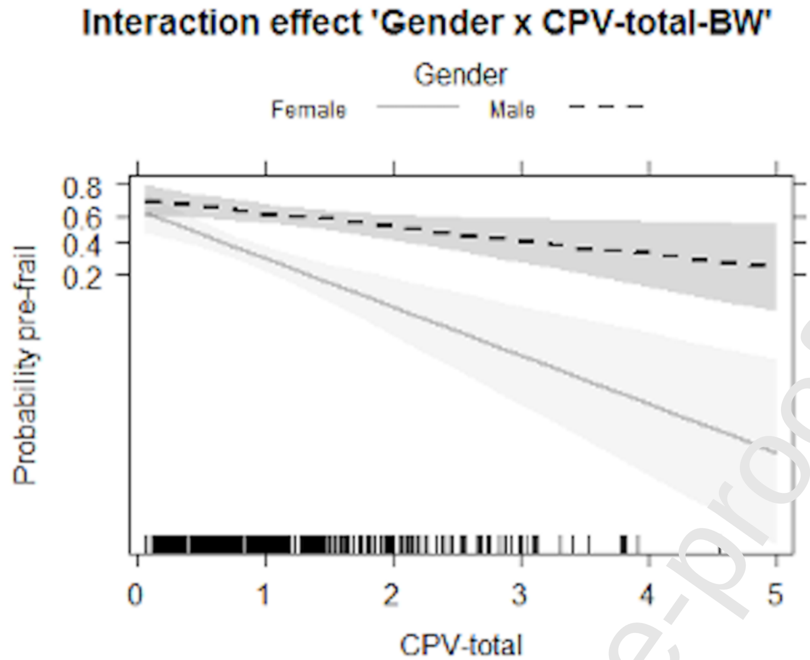
Fig 1. Flow chart.



Participants were excluded if they scored frail on one or more frailty instruments. MMSE: Mini-mental state examination, FFI: Fried Frailty Index, GFI: Groningen Frailty Index, RFI: Rockwood Frailty Index, Frail GFI & RFI: participants who scored positive on the Groningen Frailty Index and Rockwood Frailty Index, Frail GFI & FFI: participants who scored positive on the Groningen Frailty Index and Fried Frailty Index, Frail RFI, GFI, FFI: participants who scored positive on the Rockwood Frailty Index, Groningen Frailty Index *and Fried Frailty Index*

Fig. 2. Plot of the interaction between gender and CPV-total ratio on the predictive value of pre-frailty.



This figure shows the interaction factor between gender and CPV-total that was found in the logistic regression analysis. The likelihood for pre-frailty is lower for women compared to men. With an increased CPV ratio women are less likely to be pre-frail.

Table 1. Prevalence of Fried phenotype criteria

Variables	No (other) frailty markers			Combined with Low grip strength			Combined with Exhaustion			Combined with Low gait speed		
	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women
No frailty markers (robust)	214 52.8%	91 22.5%	123 30.4%									
Positive on Low grip strength	150 37.0%	118 29.1%	32 7.9%									
Positive on Exhaustion	9 2.2%	2 0.5%	7 1.7%	14 3.5%	8 2.0%	6 1.5%						
Positive on Low gait speed	6 1.5%	1 0.2%	5 1.3%	3 0.7%	3 0.7%	0 0%	2 0.5%	2 0.5%	0 0%			
Positive Unintentional weight	1 0.2%	0 0%	1 0.2%	6 1.5%	2 0.5%	4 1%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%

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loss												

%: Percentage; N: Number of participants; Percentages indicate the number of positive cases in the specific frailty item and in combination with other frailty items. Different combinations were present; positive on low grip strength combined with exhaustion, positive on low grip strength combined with low gait speed and positive on low grip strength combined with unintentional weight loss, positive on exhaustion combined with low gait speed and positive on exhaustion combined with unintentional weight loss.

Table 2. Participants' characteristics according to pre-frailty profile

Variables	**Robust**	**Pre-frail**		
	Robust n= 214	All Pre-Frail n= 191	Pre-frail without persons who scored positive on exhaustion n= 166	Pre-frail positive on Exhaustion CES-D+ n= 25
	Men n=91 Women n=123	**Men n=136 Women n=55**	**Men n=131 Women n=42**	**Man n=12 Woman n=13**
Age (years)	82.3±2.1	83.8±3.2†	83.7±3.2†	84.2±3.0*
Height (m)	1.6±0.1*	1.7±0.1*	1.7±0.1*^	1.6±0.1*
Weight (kg)	71.4±12.8	73.6±11.2	73.5±11.9	74.6±14.8*
Diabetes Mellitus (yes/no)[a]	21/193	23/168	16/150^	7/18
Hypertension (yes/no)[b]	124/89	117/74	98/68	19/6
Use of statins (yes/no)	87/126	71/120	61/105	10/15
Comorbidities (n)	2.8±1.5	2.9±1.6	2.9±1.6	3.4±1.5
High cholesterol (yes/no)[c]	46/168	27/164	25/141	2/23
BMI	26.2±3.3	26.6±3.9	26.4±3.6	27.2±3.5
Body fat (%)	34.6±6.3	33.0±7.0	32.7±66	36.3±6.9
MMSE	28.0±1.6	27.7±1.8	27.6±1.7	27.8±1.9
Physical activity (Kcal)[5]	6508.1±3751.6	5942.8±3846.8	6126.5±4007.5	4745.5±2273.5
Grip strength (Kpa)	65.1±16.4	52.5±14.1†	52.8±14.0†	50.8±14.9†
CRP	2.4±5.2	3.6±6.9	3.2±5.8^	6.1±11.8*
Fatigue resistance[1]	70.6±34.7	67.7±38.4	68.2±39.0	64.8±35.0
Grip work[2]	3376.4±1707.5	2714.2±1752.7†	2732.1±1696.1†	2596.3±2125.1†
Grip work corrected for body weight [2]	48.0±24.2	37.4±23.9†	37.7±23.5†	35.9±27.1†
MOB-T[1]	0 (0-1)	0 (0-2)*	0 (0-2)^	2 (0-4) †
MFI-20 total fatigue score (20-100)[2]	40 (31-49)	45 (32-56)*^	43 (31-54)*^	60 (43-68)†
MFI-20 General fatigue (4-20) [2]	8 (5-10)	9 (6-12)*^	8 (5-11)^	13 (10-15)†
MFI-20 physical	7 (5-10)	9 (5-12)*^	8 (5-11)^	12 (10-16)†

fatigue (4-20) [2]				
MFI-20 reduced activity (4-20) [2]	8 (6-11)	10 (6-13)^	9 (6-12)^	13 (10-15)†
MFI-20 reduced motivation (4-20) [2]	8 (5-11)	9 (6-11) ^	9 (6-11)^	11 (8-14)*
MFI-20 mental fatigue (4-20) [2]	7 (5-11)	8 (5-11)	8 (5-11)	7 (5-12)
CPV- total[4]	1.3±0,8	1.0±0.8†	1.0±0.8†	0.7±0.7†
CPV- general[4]	7.0±4.5	5.4±4.5†	5.6±4.5†	3.3±2.5†
CPV- physical[4]	7.4±5.0	5.6±4.9†	5.7±4.9†	3.9±4.9†
CPV- redact[4]	6.7±4.7	4.8±4.2†	5.0±4.2*	3.4±3.1†
CPV- redmot[4]	6.9±4.5	5.1±4.3†	5.2±4.3†	4.2±4.8†
CPV- mental[4]	7.2±4.8	5.4±4.3†	5.5±4.7†	5.4±5.5†

ANCOVA corrected for age and gender (except for age), values expressed as mean ± SD or median and interquartile range (IQR, P75-P25); Chi square test for ordinal data, Bonferroni post-hoc test

[+] Pre-frailty is defined by a positive score solely on this item

m: meters; kg: kilogram; %: percentage; Kcal: calories; Kpa: Kilo pascal; MOB-T: Mobility Tiredness scale; MFI-20: Multidimensional Fatigue Inventory; CPV: Capacity to Perceived Vitality [1]: 1 missing value; [2]; 2 missing values; [4]: 4 missing values; [5]: 5 missing values

*Significant different from robust (p<0.05) on all ANCOVA analysis corrected for age and sex (except for age); †Significant different from robust (p<0.001); ^ Significant different from pre-frail who scored positive on exhaustion

[a]: diabetes mellitus (DM); [b]: Hypertension (based on a positive score on item 15 of the Rockwood index); [c] High cholesterol (presence of dyslipidemia)

Table 3. Relationships between muscle endurance, self-perceived fatigue, CRP, physical activity and robustness or prefrailty.

	All participants N=405		Participants who are not fatigued on CES-D	
	Grip Work	Fried score	Grip Work	Fried score
Grip Work		-0.24†		-0.22†
Body fat (%)	-0.27 †	0.07	-0.28 †	0.05
Physical activity (Kcal)	0.12*	-0.03	0.13*	-0.01
CRP	-0,08	0.10	-0.08	0.07
MFI-20 total fatigue score (20-100)	-0.14*	0.18†	-0.13*	0.05
MFI-20 General fatigue (4-20)	-0.11*	0.19†	-0.12*	0.06
MFI-20 physical fatigue (4-20)	-0.21 †	0.22†	-0.19 †	0.09
MFI-20 reduced activation (4-20)	-0.15*	0.14*	-0.15*	0.03
MFI-20 reduced motivation (4-20)	-0.09	0.11*	-0.08	0.01
MFI-20 mental fatigue (5-20)	0.01	0.02	0.02	0.00
CPV- total		-0.26†		-0.23†
CPV- general		-0.26†		-0.21†
CPV- physical		-0.26†		-0.22†
CPV- redact		-0.25†		-0.21†
CPV- redmot		-0.24†		-0.22†
CPV- mental		-0.22†		-0.22†

Values represent Partial correlation coefficients corrected for age and sex*p<0.05, †p<0.01

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%: percentage; Kcal: calories; GW: Grip Work; MFI-20: Multidimensional Fatigue Inventory; CPV: Capacity to Perceived Vitality

Table 4. Logistic regression with GW/MFI-total score discriminating prefrailty/robustness for men and women

Men							
		Significant variables	**B**	**S.E.**	**Sig.**	**Odds ratio**	**95% confidence interval**
CPV-total	Model 1	Age	0.234	0.061	<0.001	1.264	1.122-1.423
	R^2: 0.138	CPV- total	-0.422	0.176	0.016	0.656	0.465-0.926
	Model 2	Age	0.222	0.061	<0.001	1.248	1.108-1.406
	R^2: 0.120	CPV- total	-0.342	0.178	0.055	0.711	0.501-1.008
CPV-general	Model 1	Age	0.233	0.061	<0.001	1.262	1.120-1.421
	R^2: 0.130	CPV-general	-0.065	0.031	0.035	0.937	0.882-0.995
	Model 2	Age	0.221	0.061	<0.001	1.247	1.107-1.405
	R^2: 0.113	CPV-general	-0.050	0.031	0.108	0.951	0.894-1.011
CPV-physical	Model 1	Age	0.231	0.061	<0.001	1.260	1.118-1.419
	R^2: 0.130	CPV-physical	-0.059	0.028	0.035	0.943	0.893-0.996
	Model 2	Age	0.219	0.061	<0.001	1.245	1.105-1.403
	R^2: 0.114	CPV-physical	-0.046	0.028	0.104	0.955	0.904-1.009
CPV-redact	Model 1	Age	0.239	0.062	<0.001	1.270	1.126-1.433
	R^2: 0.144	CPV-redact	-0.085	0.032	0.009	0.919	0.862-0.979
	Model 2	Age	0.227	0.062	<0.001	1.254	1.112-1.415
	R^2: 0.126	CPV-redact	-0.071	0.033	0.030	0.932	0.874-0.933
CPV-redmot	Model 1	Age	0.237	0.061	<0.001	1.267	1.124-1.428
	R^2: 0.140	CPV-redmot	-0.079	0.032	0.013	0.924	0.868-0.983
	Model 2	Age	0.224	0.061	<0.001	1.251	1.110-1.410
	R^2: 0.123	CPV-redmot	-0.065	0.032	0.042	0.937	0.880-0.998
CPV-mental	Model 1	Age	0.233	0.060	<0.001	1.263	1.122-1.422
	R^2: 0.138	CPV-mental	-0.071	0.030	0.018	0.931	0.878-0.988
	Model 2	Age	0.220	0.061	<0.001	1.246	1.106-1.404

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	R^2: 0.122	CPV-mental	-0.061	0.030	0.045	0.941	0.886-0.999
Women							
CPV-total	Model 1	Age	0.245	0.073	0.001	1.278	1.107-1.474
	R^2: 0.279	CPV- total	-1.495	0.344	<0.001	0.224	0.114-0.440
	Model 2	Age	0.208	0.077	0.007	1.231	1.059-1.431
	R^2: 0.290	CPV- total	-1.757	0.417	<0.001	0.173	0.076-0.391
CPV-general	Model 1	Age	0.240	0.071	0.001	1.272	1.106-1.463
	R^2: 0.292	CPV-general	-0.294	0.068	<0.001	0.745	0.653-0.851
	Model 2	Age	0.210	0.075	0.005	1.234	1.064-1.431
	R^2: 0.271	CPV-general	-0.296	0.075	<0.001	0.744	0.642-0.862
CPV-physical	Model 1	Age	0.247	0.074	0.001	1.280	1.108-1.480
	R^2: 0.292	CPV-physical	-0.271	0.063	<0.001	0.763	0.674-0.863
	Model 2	Age	0.210	0.079	0.008	1.234	1.056-1.441
	R^2: 0.327	CPV-physical	-0.355	0.082	<0.001	0.701	0.597-0.823
CPV-redact	Model 1	Age	0.227	0.070	0.001	1.255	1.094-1.440
	R^2: 0.241	CPV-redact	-0.234	0.060	<0.001	0.791	0.703-0.890
	Model 2	Age	0.195	0.074	0.008	1.215	1.051-1.404
	R^2: 0.227	CPV-redact	-0.248	0.070	<0.001	0.780	0.680-0.895
CPV-redmot	Model 1	Age	0.241	0.071	0.001	1.272	1.106-1.463
	R^2: 0.229	CPV-redmot	-0.220	0.059	<0.001	0.802	0.714-0.901
	Model 2	Age	0.205	0.075	0.006	1.228	1.059-1.424
	R^2: 0.255	CPV-redmot	-0.289	0.075	<0.001	0.749	0.646-0.868
CPV-mental	Model 1	Age	0.240	0.070	0.001	1.272	1.110-1.458
	R^2: 0.209	CPV-mental	-0.191	0.054	<0.001	0.826	0.743-0.917
	Model 2	Age	0.225	0.076	0.003	1.252	1.079-1.454
	R^2: 0.268	CPV-mental	-0.293	0.073	<0.001	0.746	0.647-0.860

Logistic regression analysis to predict pre-frailty in men and women separately; Model 1: All participants included n= 405; Model 2: Participants who are not fatigued on CES-D; R2: R square