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Research Article

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

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HIGHLIGHTS:

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

1 **ABSTRACT**

2 **Introduction:** Low muscle endurance and high feelings of self-perceived fatigue could be an early characteristic
3 of decline in intrinsic capacity, which comes to full expression as physical frailty in a later stage. This study aimed
4 to investigate if the combination of muscle endurance and self-perceived fatigue is related to pre-frailty in well-
5 functioning older adults aged 80 and over.

6
7 **Methods:** Four-hundred and five community-dwelling older adults aged 80 and over (214 robust and 191 pre-
8 frail) were assessed for muscle endurance (Grip Work corrected for body weight (GW_bw)), self-perceived
9 fatigue (MFI-20) and frailty state (Fried Frailty Index, FFI). A Capacity to Perceived Vitality (CPV) ratio was
10 calculated by dividing GW_bw by the MFI-20 scores. ANCOVA analysis (corrected for age and gender) was used
11 to compare robust and pre-frail older adults, and binary logistic regressions were applied to analyze the
12 relationship between CPV and pre-frailty status.

13
14 **Results:** Pre-frail older adults who scored negative on the exhaustion item of the FFI still showed significantly
15 lower GW_bw ($p < 0.001$), CPV ratios ($p < 0.001$) and higher self-perceived fatigue ($p < 0.05$) compared to the robust
16 ones. The risk for pre-frailty related significantly to higher age, being male and lower CPV ratios. In females,
17 every unit increase in CPV ratio decreased the risk for pre-frailty by 78% (OR 0.22; 95% CI: 0.11-0.44), for males
18 this effect was less strong (34%, OR 0.66; 95% CI: 0.47-0.93).

19
20 **Conclusions:** Pre-frail community-dwelling persons aged 80 years and over without clinical signs of exhaustion
21 on the FFI still experience significantly higher fatigue levels (lower muscle endurance, higher self-perceived
22 fatigue and lower CPV levels) compared to robust ones. CPV ratio could therefore be a good tool to identify
23 subclinical fatigue in the context of physical (pre-)frailty.

24
25 **Keywords:** Fatigue; Tiredness; Muscle Endurance; Pre-frailty; Community-dwelling; Elderly; Vitality

26
27

28 **1. INTRODUCTION**

29 Frailty is a sign of losses in reserve capacity and can be conceptually defined as "*a clinical state in which there is*
30 *an increase in an individual's vulnerability to develop negative health-related events (including disability,*
31 *hospitalizations, institutionalizations, and death) when exposed to endogenous or exogenous stressors"* (Vella-
32 azzopardi and others 2016). As a consequence, the frail person is at increased risk for different negative health
33 outcomes such as disability, hospitalization and death (Vermeiren and others 2016). A widely accepted approach
34 for the assessment of frailty consists of five components as described by Fried and others (2001): exhaustion,
35 unintentional weight loss, low physical activity, slow walking and low grip strength. Fatigue, muscle atrophy
36 (defined as sarcopenia) and muscle weakness (defined as dynapenia) are key elements in this phenotype. In the
37 pathophysiology of frailty, sarcopenia, fatigue and inflammation have been recognized to play a predominant
38 role (Bauer and Sieber 2008). Altogether, fatigue characterizes the depletion of physiological reserve capacity
39 leading to a higher risk for negative health outcomes (Knoop and others 2021). However, it is unclear when
40 fatigue plays a role in the development of frailty. Research on the occurrence of fatigue in the early stages of
41 frailty is crucial, as frailty is believed to be reversible at this stage.

42
43 Generally speaking, fatigue can be divided into self-perceived feeling of fatigue and resistance to physical
44 tiredness which includes a fatigue assessment such as muscle fatigability. A recent systematic review showed
45 that fatigue has a prominent role in the operationalization of frailty and is included in most frailty scales (Knoop
46 and others 2019). The different frailty instruments described in the literature cover a great diversity in fatigue
47 constructs reflecting different underlying pathophysiological mechanisms by which fatigue relates to frailty. The
48 fact that fatigue is a prominent element in the concept of frailty might be explained by the involvement of a
49 chronic low-grade inflammatory profile (CLIP), considered as an important parameter in the pathogenesis of
50 both fatigue and frailty (Hubbard and Woodhouse 2010; Krabbe and others 2004). Higher levels of circulating
51 inflammatory markers such as C-reactive protein (CRP) are seen in older persons who are identified with physical
52 frailty and sarcopenia (Marzetti and others 2019). Inflammation promotes sickness behaviour with fatigue as
53 one of the symptoms (Dantzer and Kelley 2007) and is related to physical limitations and frailty (Cao Dinh and
54 others 2019; Walston 2002).

55
56 Muscle endurance and self-perceived fatigue provide complementary information in well-functioning older
57 people (Bautmans and others 2010; Bautmans and others 2008). Recent research has shown that fatigue is one
58 of the early characteristics of frailty as signs of fatigue are already present approximately nine years prior to the
59 occurrence of frailty (Stenholm and others 2019). However, it is unclear whether the combination of low muscle
60 endurance and high self-perceived fatigue reflects an increased risk for the loss of reserve capacity, which comes
61 to full expression as physical frailty. It is conceivable that good muscle endurance and low self-perceived fatigue
62 outweigh the deficits in reserve capacity, thus conserving the robust and independent state. It is clinically
63 relevant to identify early predictors for physical (pre-)frailty to start preventive interventions. Once an advanced
64 frailty state is attained, it is very difficult to reverse to a robust state. Therefore, this study aimed to investigate

65 if the combination of muscle endurance and self-perceived fatigue is related to pre-frailty in well-functioning
66 older adults aged 80 and over.

67

68 **2. METHODOLOGY**

69 *2.1 Study design:*

70 Baseline data were used from the BUTTERFLY study (Brussels Study on The Early Predictors of Frailty) (Cao Dinh
71 and others 2019; Vermeiren and others 2019), involving a cohort of community-dwelling older adults aged 80
72 and over, organized by the Vrije Universiteit Brussel (Belgium). This study was approved by the ethical
73 committee of UZ Brussel (B.U.N. 143201421976), all participants signed informed consent.

74

75 *2.3. Setting and participants*

76 Four-hundred-ninety-four community-dwelling adults aged 80 years and over were recruited to participate in
77 the BUTTERFLY study. The participants were recruited through advertisements via websites of the University
78 Hospital in Jette in Belgium, general practitioners, pharmacies and health insurance companies. Participants
79 were eligible for the study if they were aged 80 and over, could walk independently, lived independently, if they
80 were mentally fit (MMSE>23/30), and not frail according to the Groningen Frailty Indicator (GFI<4/15) (Steverink
81 and others 2001), Rockwood Frailty Index (RFI<0.25/10) (Collerton and others 2012), and/or the adapted Fried
82 Frailty Index (FFI<3/4) (Sirola and others 2011); (exhaustion, weight loss, gait speed, and grip strength).
83 Participants were excluded if they underwent surgery or any radiotherapy or chemotherapy during the past six
84 months. Participants with CRP >10 mg/L were excluded, as this refers to an acute inflammatory state and not to
85 a chronic low-grade inflammatory profile (Sproston and Ashworth 2018).

86

87 *2.4. Measurements*

88 *2.4.1 Frailty score*

89 As reported previously (Cao Dinh and others 2019), the adapted version of the physical phenotype of frailty as
90 proposed by Sirola and others (2011) was used to determine frailty by a combination of 4 components:
91 unintentional weight loss, exhaustion, weakness and low gait speed. Weight loss was evaluated by the self-
92 reported question: "In the last six months, have you lost more than 4.5 kg unintentionally?" which was answered
93 by yes (1) or no (0) (Fried and others 2001). Exhaustion was measured similarly to the original Fried phenotype,
94 questioning two statements from the CES-D Depression Scale (Orme and others 1986): "I felt that everything I
95 did was an effort" and "I could not get going". The participants were asked: "How often in the last week did you
96 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
97 moderate amount of time, or (3) for most of the time. When participants scored a 2 or 3 on either of the two
98 statements, they received a point on the frailty scale for exhaustion. Gait speed was measured by timing the
99 walked distance of 4.5 m and was stratified for gender and height, as proposed by Fried and others (2001).
100 Participants were scored a point for slow walking if their walking time was ≥ 7 seconds in men ≤ 173 cm and
101 women ≤ 159 cm, and if their time was ≥ 6 seconds in men > 173 cm and women > 159 cm. Grip strength was
102 assessed using the Martin Vigorimeter; cut-offs were 42 kPa for women and 71 kPa for men (Cao Dinh and others

103 2019). Participants showing a grip strength below these cut-offs received a point for this item. In analogy to the
104 original version (Fried and others 2001), the following scoring system was put forward to assign the level of
105 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
106 considered frail.

107

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

109 Participants performed a maximal handgrip strength (GSmax) and a Fatigue resistance (FR) performance test
110 using a Martin Vigorimeter (KLS Martin Group, Tuttlingen Germany). The Martin Vigorimeter is provided with 3
111 different sizes of compressible rubber bulbs. For this study the large bulb was used as described previously
112 (Bautmans and others 2007; Bautmans and Mets 2005). Briefly, the participants were asked to squeeze the bulb
113 (with the dominant hand) three times as hard as possible, the highest score of the three attempts was registered
114 as GSmax. Afterwards, the FR was measured by asking the participants to squeeze in the bulb as hard as possible
115 and to maintain this maximal effort as long as possible, under standardized verbal stimulation by the
116 investigator. The time in seconds during which the GSmax dropped to 50% of its maximum was recorded as FR.
117 These two parameters were used to calculate Grip Work (GW) by multiplying FR in seconds by 75% of the GSmax
118 ($GW = 0.75 * GSmax * FR$) (Bautmans and others 2007). GW was also corrected for body mass (GW/body mass
119 in kg) since overweight and obese participants will have to engage more strength and sustain that higher effort
120 over time to execute their daily tasks (Bautmans and others 2011).

121

122 *2.4.2 Self-perceived fatigue*

123 The Multidimensional Fatigue Inventory (MFI-20) was used to assess the level of self-perceived fatigue. The MFI-
124 20 is a self-reported fatigue questionnaire consisting of twenty items that cover five domains of fatigue: (1)
125 general fatigue, (2) physical fatigue, (3) reduction in activity, (4) reduction in motivation, (5) cognitive fatigue
126 (Smets and others 1995). If more than half of the items were missing, items were substituted by the mean of
127 the non-missing items. Items are scored on a five-point Likert scale, a higher score (20-100) indicates higher
128 fatigue and vice versa. In addition, the Mobility Tiredness scale- designed to measure mobility-related fatigue in
129 older adults – was used. It is questionnaire-based and counts the number of items where the participant
130 reported tiredness after performing six activities; indoor transfers, walk indoors, go outdoors, walk outdoors in
131 nice weather and walk outdoors in poor weather, and climb stairs. Low score refers to low fatigue and vice versa
132 (Avlund and others 1993).

133

134 *2.4.3 Inflammation*

135 Non-fasting blood samples were taken by venepuncture on the day of assessment, before performing the
136 physical tests. Circulating level of C-reactive protein (CRP) was obtained by nephelometry (Behring, Marburg,
137 Germany). When measurements of CRP fell below the LOD (Lower limits of detection <0.5) (n=53), we imputed
138 values from a uniform distribution between 0 and the LOD.

139

140 *2.4.4 Anthropometry, body composition & Physical activity*

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

149

150 2.5. Statistical analysis.

151 Statistical analyses were performed using Statistical Package of the Social Sciences (SPSS) version 26 (IBM,
152 Amonk, New York, USA) and the statistical software RStudio version 1.1.463 running on R version 3.5.3 (R
153 Foundation for Statistical Computing, Vienna, Austria). Significance was set a priori at two-sided $p < 0.05$.
154 Average values are presented with mean \pm standard deviation (SD) or median \pm interquartile range (IQR, P75-
155 P25) depending on measurement level and normality of distribution. Firstly, the prevalence of positive frailty
156 components of the FFI are presented as percentages (expressing the number of positive cases divided by the
157 number of the total study population). Secondly, differences in age between robust and pre-frail older adults
158 were investigated by the independent samples T-test. Thirdly, differences between robust and pre-frail older
159 adults (divided into categories based on the positive items of the FFI: (a) pre-frail based on low grip strength, (b)
160 pre-frail based on exhaustion, (c) pre-frail based on weight loss, (d) pre-frail based on slow walking speed) were
161 explored by one-way Analysis of Covariance (ANCOVA). We hypothesized that the relations between muscle
162 endurance, self-perceived fatigue and frailty status might be influenced by sex and age (Collard and others 2012),
163 and thus we corrected for these variables. Next, partial Pearson correlations (corrected for age and sex) were
164 computed to determine the association between frailty score and fatigue (GSmax, FR, GW corrected for body
165 mass, self-perceived fatigue, CPV ratio and CRP). Then, binary logistic regression analysis using forward selection
166 was conducted to assess whether the variables (age, BMI, CRP, body fat, GW and MFI-20 as independent factors)
167 discriminated between robustness and pre-frailty, and odds ratios were calculated. Non-significant parameters
168 were not used in the final models. The presented p values in table 4 are based on the Wald test. To test the
169 hypothesis whether persons with low muscle fatigability and high feelings of self-perceived fatigue are more
170 likely to be pre-frail, we investigated the interaction between muscle fatigability and self-perceived fatigue
171 ($GW_{\text{corrected for body weight}} * 1/MFI-20$) on the occurrence of pre-frailty. Since a high score on the GW is considered to
172 be good, as well as a low score on the MFI-20, a classic interaction computation as the product of these
173 parameters would neutralize the linear increase in interaction score with combined worsening scores on muscle
174 fatigability and self-perceived fatigue. Therefore, we recomputed the MFI-20 scores as $1/MFI-20$ for testing its
175 interaction with GW. All these interactions significantly predicted pre-frailty. To better interpret this interaction,
176 a “Capacity to Perceived Vitality” ratio (CPV) ratio was computed as $GW_{\text{corrected for body weight}} / MFI-20$, resulting in
177 high ‘combined’ fatigue levels when the ratio was low, and low ‘combined’ fatigue levels when the ratio is high.
178 In total 5 different ratios were computed, CPV-total ($GW_{\text{corrected for body weight}} / MFI-20$ total fatigue), CPV-general

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

192

193 **3. RESULTS**

194 This study included 405 participants (mean age 83 ± 3 years, flowchart shown in Fig. 1) among which 214 robust
195 (91 males and 123 females) and 191 pre-frail (136 males and 55 females) older adults. Pre-frail participants were
196 significantly older than their robust counterparts (respectively 84 ± 3 and 82 ± 2 years, $p < 0.001$). Low grip strength
197 is the most prevalent positive frailty criterion in the pre-frail older adults, followed by exhaustion and low gait
198 speed (see table 1.). Twenty-five participants scored positive on more than one frailty criterion, of whom 14 on
199 exhaustion combined with low grip strength (see table 1).

200

201 The participants’ characteristics are shown in table 2. Robust participants had significantly higher GW ($p < 0.001$),
202 less fatigue on the MOB-T ($p < 0.05$) and MFI-20 (total, general, physical) ($p < 0.05$) and better CPV ratios ($p < 0.001$).
203 Pre-frail older adults who scored negative on the exhaustion item of the FFI index still showed lower levels of
204 GW ($p < 0.001$) and CPV ratios ($p < 0.001$), and higher levels on the MFI-20-total ($p < 0.05$), MFI-20 physical fatigue
205 ($p < 0.05$), MFI-20 general fatigue ($p < 0.05$) and MOB-T ($p < 0.05$) compared to their robust counterparts. When
206 looking at pre-frail adults who scored positive on the exhaustion item of the FFI, it can be seen that they also
207 scored lower on all muscle fatigue and CPV levels, and higher on self-perceived fatigue (except of MFI-20 mental
208 fatigue).

209

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

215 A binary logistic regression was performed per CPV ratio (sub)scale with pre-frailty as dependent variable (table
216 4 and supplementary table 1). The regression analyses indicated that in all models age and the interaction

217 between sex and CPV ratios were significantly associated with pre-frailty. CRP, physical activity and percentage
218 body fat, did not significantly contribute and thus were not retained in the final models. The risk for being pre-
219 frail increases with age and decreases with a higher CPV ratio. A significant interaction between CPV ratios and
220 sex was found (supplementary table 1). Figure 2 shows this interaction and indicates that with increasing CPV
221 ratio, the risk for pre-frailty decreases more for females compared to males. For a better clinical interpretation
222 of this interaction, we performed the same analyses for males and females separately (table 4). In our study,
223 males have a higher risk to be pre-frail compared to females. With increasing CVP ratio, the risk for pre-frailty
224 decreases significantly. These results were found for all CPV ratios and the visualisations of these effects are
225 shown in supplementary Figures 1a-2f. A separate logistic regression was performed per gender; in females
226 every unit increase in fatigue ratio showed to decrease the risk for pre-frailty with 77.6% (CPV total model 1 OR
227 0.224; 95% CI: 0.114-0.440). In males these results were also present but less strong as for females (34,4%; CPV
228 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
229 slightly higher when excluding persons who scored negative on the CES-D item for males (model 1 OR 0.656;
230 95% CI: 0.465-0.926: model 2 OR 0.711; 95% CI: 0.501-1.008), for females we found the opposite (model 1 OR
231 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
232 evaluate and visualize the fit of the logistic regression for all total models (supplementary Figures 3a- 3L). The
233 highest AUC was observed for CPV-physical ratio (AUC: 0.782, see supplementary table 1).

234

235 4. **DISCUSSION**

236 In this study, we investigated whether the combination of muscle endurance and self-perceived fatigue is related
237 to frailty in well-functioning older adults aged 80 and over. The main finding of this study was that also in
238 participants who are pre-frail but did not show clinical signs of fatigue on the exhaustion component in the FFI,
239 still experienced significantly higher fatigue levels (lower muscle endurance, higher self-perceived fatigue and
240 lower CPV levels) compared to their robust counterparts. Logistic regression analysis showed that age, gender,
241 CPV ratio, and the interaction between CPV ratio and gender were significantly associated with pre-frailty, in
242 community dwelling octogenarians, with overall predictive accuracy of 77%. As a significant interaction was
243 found between muscle fatigue and self-perceived fatigue, we computed a CPV ratio since this value is clinically
244 more informative to interpret than the statistical interaction. Females were less likely to be pre-frail and with
245 increasing CVP ratio the risk for pre-frailty decreased significantly, for males this effect was also found but less
246 strong. Muscle endurance correlated significantly but moderately with self-perceived fatigue, suggesting that
247 both provide complementary information regarding the clinical expression of fatigue. Therefore, the interplay
248 between these two variables expressed as the CPV ratio might be a good fatigue “index” in frailty assessment.
249 All CPV ratios showed a stronger relationship with the FFI than muscle endurance and self-perceived fatigue
250 separately; and logistic regression showed that CPV ratio can discriminate between robust and pre-frailty status.
251 Results showed that age and the CPV ratio were significantly associated to the frailty status, even when the pre-
252 frail participants did not score positively on the fatigue item in the FFI.

253

254 In this study we found that low muscle endurance is related to higher frailty scores, this is in line with earlier
255 research where it was shown that muscle endurance and frailty share the same biomedical determinants (i.e.
256 aging, disease, inflammation, physical inactivity, malnutrition, hormonal deficiencies, subjective fatigue and
257 neuromuscular function and structure) (Theou and others 2008). Also, both muscle endurance and self-
258 perceived fatigue are part of the “vicious cycle of frailty” as proposed by Fried and others (2004). The group of
259 Westerblad showed that muscle endurance decreases before the onset of muscle weakness in a mouse model
260 of premature aging (Yamada and others 2012). This implies that low muscle endurance is probably an important
261 early marker for frailty (Kent-Braun and others 2002). Thereby, it has been shown that muscle endurance can
262 help to discriminate older women with different degrees of frailty (De Dobbeleer and others 2018). Interestingly,
263 we found significant differences in self-perceived fatigue and muscle endurance between robust and pre-frail
264 participants, also within participants who scored negatively for the exhaustion item in the FFI. This could imply
265 that persons who do not score positively on exhaustion in the FFI show already early signs of fatigue. However,
266 this was not detected by the CES-D questions, one of the key elements in the FFI (Orme and others 1986). The
267 CES-D items in the FFI were included by Fried and others (2001) assuming that they indicate exhaustion,
268 comprising low energy and poor endurance. These CES-D items are associated with the VO₂max and are able to
269 predict cardiovascular disease (Fried and others 2001). Multiple adapted FFI versions used other fatigue
270 instruments to capture the exhaustion item including generic questions such as feeling tired or feeling worn out,
271 and questions from the 36-item Short Form Health questionnaire (Knoop and others 2019). Despite the large
272 array of operationalization, all exhaustion items belong to the same ICF category (Azzopardi and others 2016).
273 However, it is questionable if these tools are capable to detect early stages of fatigue. In our study, we found
274 that participants show already signs of losses in reserve capacity expressed by a low CPV ratio before they score
275 positive on the CES-D exhaustion items. Therefore, it can be hypothesized that including a measurement of
276 muscle endurance in combination with self-perceived fatigue can be a valuable asset in early physical frailty
277 identification. This will help developing preventive and therapeutic interventions.

278
279 In contrast to other studies (Cao Dinh and others 2019; Walston 2002), we did not find a significant relationship
280 between inflammation and frailty status. In addition, no significant relationship was found between CRP and
281 muscle endurance. These results are contradictory to other articles that showed a relationship with
282 inflammation in community-dwelling older persons (Bautmans and others 2007; Beyer and others 2012a) and
283 in hospitalized geriatric patients (Arnold and others 2017; Beyer and others 2012b). However, literature in
284 healthy community-dwelling older adults is scarcer, which could explain the lack of similar findings. In our study,
285 we included relatively healthy, high performing participants who were not frail and who performed sufficient
286 physical activity, which might decrease the risk for inflammaging. As CRP was used to exclude participants with
287 ongoing inflammatory pathology; not primarily to quantify low-grade inflammation we did not use high
288 sensitivity (hs)CRP. Therefore, we might have missed the influence of low-grade inflammation in our statistical
289 analysis.

290

291 We hypothesized that fatigue is a valid parameter for intrinsic capacity, a concept introduced by the World
292 Health Organization (WHO). Intrinsic capacity expresses all physical and mental capacities of an individual (Cesari
293 and others 2018). Intrinsic capacity and the loss of reserve capacity as seen in frailty (Baerd JR 2019) are highly
294 interrelated. Where intrinsic capacity is more presenting the reserves of an individual, frailty focuses more on
295 the deficit accumulation with ageing (Fried and others 2001). Reduced intrinsic capacity will have implications
296 on the level of physical functioning. The WHO suggests that changes in intrinsic capacity are likely to start at
297 midlife, before persons will experience problems in daily functioning. It is hypothesized that some parameters
298 will influence the depletion of reserve capacity leading to enlarged risk for frailty. The combination of high self-
299 perceived fatigue and low muscle endurance could be recognized as deficits modifying intrinsic capacity and
300 partly determine the development of frailty. However, the exact role of these two parameters in this concept
301 has not been investigated before. The results of this study show that muscle fatigue and self-perceived fatigue
302 are a good indicator for early stages of pre-frailty. Males were more likely to be pre-frail in this cohort, especially
303 those with a low CPV ratio. This is in contrast with earlier research where females were more likely to be pre-
304 frail (Collard and others 2012; Gordon and others 2017). However, this is the first report on persons aged 80 and
305 over. Since in our sample there were more males than females, this could have influenced the results. Females
306 with better CPV ratios are less likely to be pre-frail; in males the same results were found but the effects were
307 less strong. This suggests that the level of fatigue might be more important for females in the pathophysiology
308 for frailty, considering that other characteristics are involved in males and females.

309
310 As far as we know, this is the first study suggesting that the CPV ratio could be an additional characteristic in the
311 early identification of physical frailty. However, our study is based on cross-sectional data, and the results should
312 be confirmed prospectively. The ROC curves found in this study show acceptable to good AUC value (range 0.755
313 – 0.782)(Mandrekar 2010), suggesting a decent prediction of pre-frailty. For clinical practice, the results showed
314 that robust older adults showed on average a CPV total score >1, while pre-frail older adults had on average a
315 score <1. Every unit increase of CPV score decreased the risk for pre-frailty with 34% for males and 78% for
316 females.

317
318 This study has certain strengths and limitations. The strength of this study relies in the inclusion of a relatively
319 large and unique cohort considering the age and independence level of the participants, providing unique data
320 on potentially early determinants of frailty. It cannot be excluded that the lack of statistical differences and
321 relationships between frailty status and inflammation is due to the fact that on the one hand we recruited
322 participants without ongoing inflammatory pathology, and on the other hand that the CRP-assay lacked
323 sensitivity. The finding that males were more likely to be pre-frail might be due to an uneven distribution of
324 males and females in our study sample. However, the relationship between fatigue and frailty status was similar
325 when analysing female and male separately. The total accuracy rate of the models leaves room for improvement
326 and implies that other variables should be included in the early detection of physical frailty. However, we have
327 included percentage body fat, physical activity and inflammation, but these parameters did not contribute
328 significantly. On the other hand, it might be possible that the CPV captures a phenotype that is not completely

329 detected by the FFI. Finally, all findings in this study are based on a cross-sectional analysis, and prospective
330 confirmation is advocated, as pre-frailty is an unstable condition and reverse causation cannot be excluded.

331

332 **5. CONCLUSION**

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

340

341 **6. STATEMENTS**

342 **6.3. Acknowledgement**

343 N/A

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345 **7.1 Statements of ethics**

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

348

349 **7.2 Conflict of interest**

350 The authors have no relevant conflicts of interest to declare.

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355

356 **7.3 Author Contributions**

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

361 **Group**

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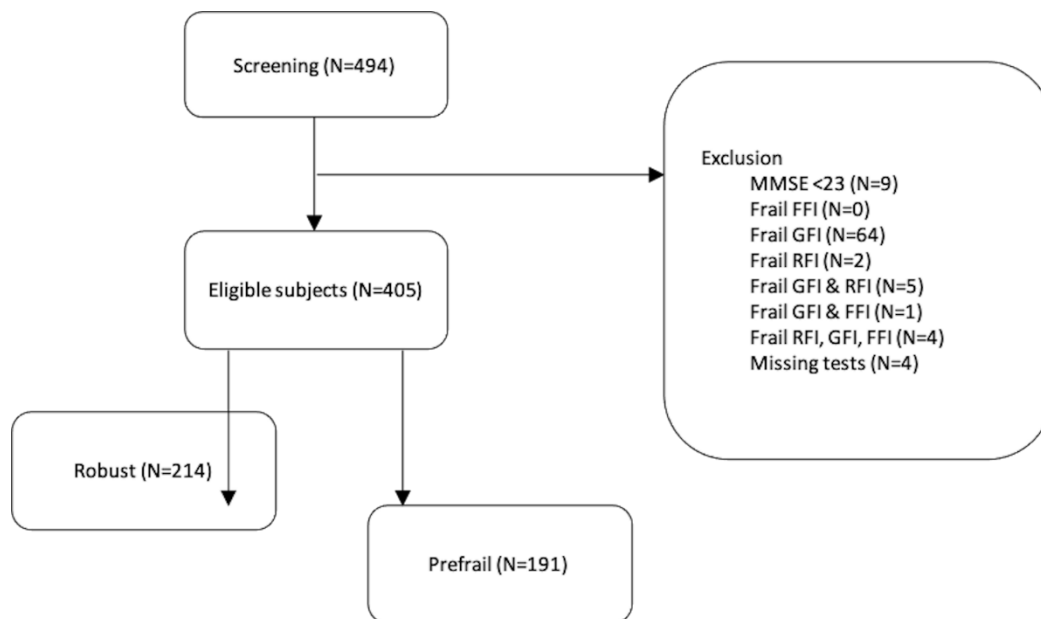
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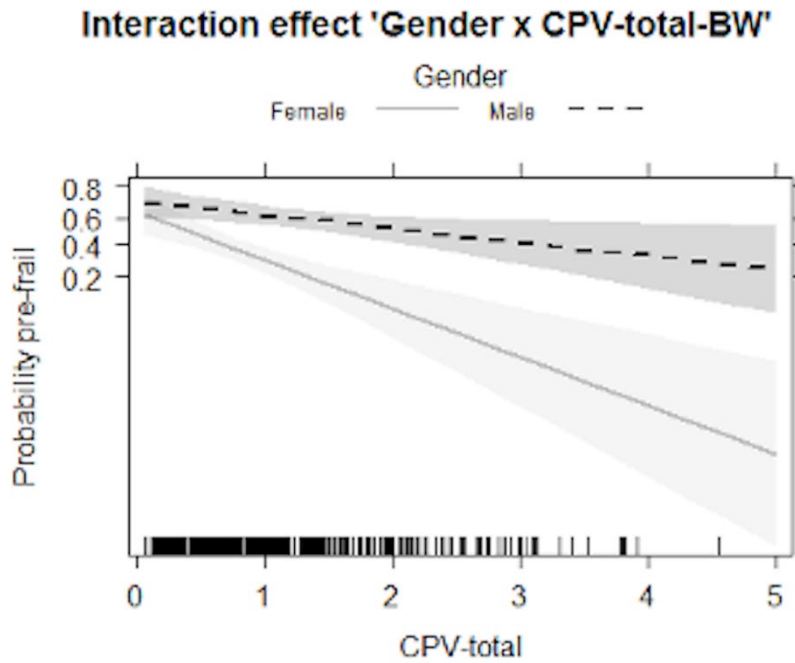
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Fig 1. Flow chart.

MMSE: Mini-mental state examination, FFI: Fried Frailty Index, GFI: Groningen Frailty Index, RFI: Rockwood Frailty Index



503 **Fig. 2. Plot of the interaction between gender and CPV-total ratio on the predictive value of pre-frailty.**
 504 *This figure shows the interaction factor between gender and CPV-total that was found in the logistic regression*
 505 *analysis. The risk for pre-frailty is lower for females compared to males. With an increased CPV ratio decreased*
 506 *the chance to be pre-frail for females.*
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511 **Table 1. Prevalence of Fried phenotype criteria**
 512

Variables	No (other) frailty markers			Combined with Low grip strength			Combined with Exhaustion			Combined with Low gait speed		
	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
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 loss	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%

513
 514 %: Percentage; N: Number of participants; Percentages indicate the number of positive cases in the specific
 515 frailty item and in combination with other frailty items. Different combinations were present; positive on low
 516 grip strength combined with exhaustion, positive on low grip strength combined with low gait speed and
 517 positive on low grip strength combined with unintentional weight loss, positive on exhaustion combined with
 518 low gait speed and positive on exhaustion combined with unintentional weight loss.

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

Variables	Robust	Pre-frail				
	Robust n= 214	Pre-Frail n= 191	Positive on Low grip strength n= 173	Positive on Low gait speed n= 11	Positive on Exhaustion CES-D n= 25	Positive Unintentional weight loss n= 7
	Males n=91 Females n=123	Males n=136 Females n=55	Males n=131 Females n=42	Males n=6 Females n=5	Males n=12 Females n=13	Males n=2 Females n=5
Age (years)	82.30±2.13	83.79±3.15 [†]	83.76±3.08 [†]	83.84±3.81 [†]	84.23±3.03*	82.38±3.22
Height (m)	1.6±0.1*	1.7±0.1*	1.7±0.1 [†]	1.7±0.1*	1.6±0.1*	1.6±0.1*
Weight (kg)	71.4±12.8	73.6±11.2	73.9±11.1	72.4±12.8	74.6±14.8*	65.2±12.8
BMI	26.2±3.3	26.6±3.9	26.8±3.4	23.8±8.4*	27.2±3.5	24.5±2.7
Body fat (%)	34.6±6.3	33.0±7.0	32.5±6.8	33.9±8.7	36.3±6.9	34.3±5.0
MMSE	28.0±1.6	27.7±1.8	27.5±1.8	27.5±1.6	27.8±1.9	27.7±1.7
Physical activity (Kcal) ⁵	6496.0±3747.0	5942.8±3846.8	6093.1±3967.3	5256.6±3120.3	4745.5±2273.5	6455.8±4164.1
Grip strength (Kpa)	65.1±16.4	52.5±14.1 [†]	51.9±13.8 [†]	60.3±15.3 [†]	50.8±14.9 [†]	47.9±19.3 [†]
CRP	2.4±5.2	3.6±6.9	3.6±7.1	1.7±1.8	6.1±11.8*	3.8±4.1
Fatigue resistance ¹	70.6±34.7	67.7±38.4	68.1±38.8	60.7±42.4	64.8±35.0	61.2±32.6
Grip work ²	3376.4±1707.5	2714.2±1752.7 [†]	2685.9±1683.1 [†]	2966.3±2683.0 [†]	2596.3±2125.1 [†]	1976.2±824.8 [†]
Grip work corrected for body weight ²	48.0±24.2	37.4±23.9 [†]	37.0±23.3 [†]	41.3±34.2 [†]	35.9±27.1 [†]	30.9±13.7 [†]
MOB-T ¹	0 (0-1)	0 (0-2)*	0 (0-2)	2 (0-3)*	2 (0-4) [†]	0 (0-1)*
MFI-20 total fatigue score (20-100) ²	40 (31-49)	45 (32-56)*	44 (32-55)	52 (45-61)*	60 (43-68) [†]	31 (26-58)
MFI-20 General fatigue (4-20) ²	8 (5-10)	9 (6-12)*	8 (5-11)*	10 (9-13)*	13 (10-15) [†]	9 (5-9)*
MFI-20 physical fatigue (4-20) ²	7 (5-10)	9 (5-12)*	8 (5-11)*	11 (9-13) [†]	12 (10-16) [†]	6 (5-12)*
MFI-20 reduced activity (4-20) ²	8 (6-11)	10 (6-13)	10 (6-13)	11 (9-13)	13 (10-15) [†]	8 (4-13)
MFI-20 reduced motivation (4-20) ²	8 (5-11)	9 (6-11)	9 (6-11)	11 (8-12)	11 (8-14)*	7 (6-10)
MFI-20 mental fatigue (4-20) ²	7 (5-11)	8 (5-11)	8 (5-11)	7 (5-10)	7 (5-12)	5 (4-12)
CPV- total ⁴	1.3±0.8	1.0±0.8 [†]	1.0±0.8 [†]	0.8±0.5 [†]	0.7±0.7 [†]	0.9±0.4 [†]
CPV- general ⁴	7.0±4.5	5.4±4.5 [†]	5.3±4.5 [†]	3.8±2.6 [†]	3.3±2.5 [†]	4.4±2.2 [†]
CPV- physical ⁴	7.4±5.0	5.6±4.9 [†]	5.6±4.9 [†]	3.5±2.5 [†]	3.9±4.9 [†]	4.4±2.0 [†]
CPV- redact ⁴	6.7±4.7	4.8±4.2 [†]	4.8±4.2 [†]	3.8±2.6 [†]	3.4±3.1 [†]	4.7±2.5 [†]
CPV- redmot ⁴	6.9±4.5	5.1±4.3 [†]	5.1±4.3 [†]	4.0±2.7 [†]	4.2±4.8 [†]	4.4±2.1 [†]
CPV- mental ⁴	7.2±4.8	5.4±4.3 [†]	5.4±4.3 [†]	5.7±4.6 [†]	5.4±5.5 [†]	5.0±2.2 [†]

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ANCOVA corrected for age and gender, values expressed as mean ± SD

Bonferroni post-hoc test

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) on all ANCOVA analysis corrected for age and sex (except for age)

553 **Table 3. Relationships between muscle endurance, self-perceived fatigue, CRP, physical activity and robustness or prefrailty.**
 554

	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 [†]

555 Values represent Partial correlation coefficients corrected for age and sex* $p < 0.05$, [†] $p < 0.01$
 556 %: percentage; Kcal: calories; GW: Grip Work; MFI-20: Multidimensional Fatigue Inventory; CPV: Capacity to Perceived Vitality
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572 Table 4. Logistic regression with GW/MFI-total score discriminating prefrailty/robustness for males and females

Males							
		Significant variables	B	S.E.	Sig.	Odds ratio	95% confidence interval
CPV- total	Model 1 R ² : 0.138	Age	0.234	0.061	<0.001	1.264	1.122-1.423
		CPV- total	-0.422	0.176	0.016	0.656	0.465-0.926
	Model 2 R ² : 0.120	Age	0.222	0.061	<0.001	1.248	1.108-1.406
		CPV- total	-0.342	0.178	0.055	0.711	0.501-1.008
CPV- general	Model 1 R ² : 0.130	Age	0.233	0.061	<0.001	1.262	1.120-1.421
		CPV- general	-0.065	0.031	0.035	0.937	0.882-0.995
	Model 2 R ² : 0.113	Age	0.221	0.061	<0.001	1.247	1.107-1.405
		CPV- general	-0.050	0.031	0.108	0.951	0.894-1.011
CPV- physical	Model 1 R ² : 0.130	Age	0.231	0.061	<0.001	1.260	1.118-1.419
		CPV- physical	-0.059	0.028	0.035	0.943	0.893-0.996
	Model 2 R ² : 0.114	Age	0.219	0.061	<0.001	1.245	1.105-1.403
		CPV- physical	-0.046	0.028	0.104	0.955	0.904-1.009
CPV- redact	Model 1 R ² : 0.144	Age	0.239	0.062	<0.001	0.270	1.126-1.433
		CPV- redact	-0.085	0.032	0.009	0.919	0.862-0.979
	Model 2 R ² : 0.126	Age	0.227	0.062	<0.001	1.254	1.112-1.415
		CPV- redact	-0.071	0.033	0.030	0.932	0.874-0.933
CPV- redmot	Model 1 R ² : 0.140	Age	0.237	0.061	<0.001	1.267	1.124-1.428
		CPV- redmot	-0.079	0.032	0.013	0.924	0.868-0.983
	Model 2 R ² : 0.123	Age	0.224	0.061	<0.001	1.251	1.110-1.410
		CPV- redmot	-0.065	0.032	0.042	0.937	0.880-0.998
CPV- mental	Model 1 R ² : 0.138	Age	0.233	0.060	<0.001	1.263	1.122-1.422
		CPV- mental	-0.071	0.030	0.018	0.931	0.878-0.988
	Model 2 R ² : 0.122	Age	0.220	0.061	<0.001	1.246	1.106-1.404
		CPV- mental	-0.061	0.030	0.045	0.941	0.886-0.999
Females							
CPV- total	Model 1 R ² : 0.279	Age	0.245	0.073	0.001	1.278	1.107-1.474
		CPV- total	-1.495	0.344	<0.001	0.224	0.114-0.440
	Model 2 R ² : 0.290	Age	0.208	0.077	0.007	1.231	1.059-1.431
		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

573 Logistic regression analysis to predict pre-frailty in males and females separately; Model 1: All participants included n= 405; Model 2: Participants who are not fatigued on
574 CES-D; R2: R square
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LEGENDS TO THE SUPPLEMENTARY FIGURES

Supplementary Fig. 1. Plots of the interaction between gender and CPV ratios on the predictive value of pre-frailty. Fig. 1a CPV-general ratio, Fig. 1b CPV-physical ratio, Fig. 1c CPV-redact ratio, Fig. 1d CPV-redmot ratio, Fig. 1e CPV-mental ratio

Supplementary Fig. 2. Plots of the interaction between gender and CPV-total ratio on the predictive value of pre-frailty in participants who were not exhausted on CES-D. Fig. 2a CPV-total ratio, Fig. 2b CPV-general ratio, Fig. 2c CPV-physical ratio, Fig. 2d CPV-redact ratio, Fig. 2e CPV-redmot ratio, Fig. 2f CPV-mental ratio

Supplementary Fig. 3. ROC Curves reflecting the discriminative value of CPV ratios for identifying pre-frailty In all participants Fig. 3a CPV-total ratio, Fig. 3b CPV-general ratio, Fig. 3c CPV-physical ratio, Fig. 3d CPV-redact ratio, Fig. 3e CPV-redmot ratio, Fig. 3f CPV-mental ratio; **and in participants who were not exhausted on CES-D** Fig. 3g CPV-total ratio, Fig. 3h CPV-general ratio, Fig. 3i CPV-physical ratio, Fig. 3j CPV-redact ratio, Fig. 3k CPV-redmot ratio, Fig. 3l CPV-mental ratio