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1 **Impairments in Hemodynamic Responses to Orthostasis Associated with Frailty: Results**  
2 **from TILDA**

3

4 Matthew DL O’Connell<sup>PhD1</sup>, George M Savva<sup>PhD2</sup>, Ciarán Finucane<sup>PhD1,3</sup>, Roman Romero-  
5 Ortuno<sup>PhD1</sup>, Chie Wei Fan<sup>MD1</sup>, and Rose Anne Kenny<sup>MD1,4</sup>

6

7 <sup>1</sup>The Irish Longitudinal Study on Ageing (TILDA), Department of Medical Gerontology, Trinity  
8 College Dublin, Ireland.

9 <sup>2</sup>School of Health Sciences, University of East Anglia, Norwich, United Kingdom.

10 <sup>3</sup>Dept. of Medical Physics and Bioengineering, Mercer’s Institute for Successful Ageing, St.  
11 James’s Hospital, Dublin, Ireland.

12 <sup>4</sup>Mercer’s Institute for Successful Ageing, St. James’s Hospital, Dublin, Ireland.

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18 Abbreviated title: Frailty and Orthostatic Blood Pressure

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23 Corresponding author:  
24 Matthew O'Connell  
25 The Irish Longitudinal Study of Ageing (TILDA)  
26 Lincoln Gate  
27 Trinity College  
28 Dublin 2  
29 Republic of Ireland  
30 Phone: +353 1 896 4392  
31 Fax: +353 1 896 2451  
32 [occonnem8@tcd.ie](mailto:occonnem8@tcd.ie)  
33  
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35 **Abstract**

36 **Background:** Dysregulated homeostatic response to stressors may underlie frailty in older  
37 adults. Orthostatic hypotension results from impairments in cardiovascular homeostasis and  
38 is implicated in falls and other adverse outcomes. This study aimed to characterise the  
39 relationships between orthostatic blood pressure (BP) and heart rate recovery and frailty in  
40 an older population.

41 **Design:** Cross-sectional study

42 **Setting:** Two health centres in the Republic of Ireland

43 **Participants:** 4334 adults aged 50 and older enrolled in The Irish Longitudinal Study on  
44 Ageing

45 **Measurements:** Continuous non-invasive BP responses during active standing were  
46 captured by Finometer<sup>®</sup>. Frailty was assessed using the Cardiovascular Health Study criteria.  
47 Linear mixed models (random intercept) with piecewise splines were used to model  
48 differences in the rate of BP and heart rate recovery.

49 **Results:** 93 (2.2%) participants were frail and 1366 (31.5%) were prefrail. Adjusting for age  
50 and sex, frailty was associated with a reduced rate of systolic BP recovery between 10-20  
51 seconds post stand (frailty\*time = -4.12 95%CI: -5.53 - -2.72) and with subsequent deficits in  
52 BP between 20-50 seconds. Similar results were seen for diastolic BP and heart rate. Further  
53 adjustment for health behaviours, morbidities, and medications reduced, but did not  
54 attenuate these associations. Of the 5 frailty criteria, only slow gait speed was consistently  
55 related to impaired BP and heart rate responses in the full models.

56 **Conclusions:** Frailty, and particularly slow gait speed, was associated with reduced rate of  
57 recovery in BP and heart rate recovery following active standing. Impaired BP recovery may  
58 represent a marker of physiological frailty.

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60 Key words

61 Frailty, Orthostatic Hypotension, Aging, Blood pressure, Homeostasis

62

63 Word count

64 Abstract: 250

65 Text: 3000

66 Number of Figures: 5

67 **Impact statement**

68 We certify that this work is novel or confirmatory of recent novel clinical research. The  
69 potential impact of this research on clinical care or health policy includes the following: it  
70 highlights the relevance of impaired blood pressure regulation as a potential cause of  
71 adverse outcomes in older adults with signs of frailty, with implications for decision making  
72 around antihypertensive treatment. The results also show that slow gait speed captures  
73 physiological frailty at least as well as the overall phenotype criteria. More broadly, they  
74 tentatively suggest rate of recovery in blood pressure immediately post standing may be a  
75 useful way to assess physiological reserve in older adults.

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## 87 Introduction

88 Levels of functional ability and risk of adverse health outcomes vary widely across older  
89 adults. This differential vulnerability among adults of the same age is often referred to as  
90 frailty.<sup>1,2</sup> Frailty can be conceptualised as a syndrome of physiological dysregulation leading  
91 to a decreased ability to respond to homeostatic stressors, and recognisable as a phenotype  
92 comprising 5 related criteria: slow gait, muscle weakness, poor endurance or exhaustion,  
93 low physical activity and loss of (lean) body weight.<sup>3</sup>

94 Few studies have directly explored the relationships between this frailty phenotype and  
95 dynamic measures of homeostatic responses. Orthostasis, or standing up, is a mild  
96 physiological stressor requiring an integrative neuro-cardiovascular response to maintain  
97 blood pressure (BP) homeostasis in the face of large shifts in blood volume distribution.<sup>4</sup>  
98 Impaired responses can lead to excessive falls in BP known as orthostatic hypotension (OH).  
99 In analogy to frailty, OH may reflect various underlying health deficits and is predictive of  
100 adverse outcomes in older adults.<sup>5,6</sup>

101 In previous studies OH, defined according to the consensus definition of a sustained drop of  
102 20mmHg in systolic BP (SBP) or 10mmHg in diastolic BP (DBP) <sup>7</sup>, was not related to physical  
103 frailty.<sup>8,9</sup> However, frailty has been associated with lower heart rate variability, another sign  
104 of impaired autonomic control of the cardiovascular system, in older women.<sup>10,11</sup>

105 Discrete BP measurements capture only a fraction of the full hemodynamic responses.

106 Studies using continuous BP monitoring suggest aging is characterised by a gradual slowing  
107 of initial BP recovery post-standing, indicative of declining BP homeostatic function.<sup>12</sup>

108 Recent data has linked impairments in early BP recovery to mortality in older falls clinic

109 patients.<sup>13</sup> Similarly, pilot data from a convenience sample of older Irish adults suggested  
110 possible relationships between orthostatic hemodynamics and frailty.<sup>14</sup>

111 We hypothesise the frailty phenotype and impaired orthostatic hemodynamics to be shared  
112 manifestations of an underlying physiological frailty. In addition, there may be direct  
113 mechanisms linking the physical frailty criteria to BP homeostasis, including loss of muscle  
114 mass and strength, impaired peripheral nerve function and/or declining central nervous co-  
115 ordination.<sup>14</sup>

116 This study aimed to characterise the BP and heart rate responses to orthostasis across levels  
117 of frailty within a large population sample of middle-aged to older adults and to assess the  
118 role of health conditions and medications in these relationships. We further aimed to  
119 explore the relationships between hemodynamic responses and the different frailty criteria.

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129 **Methods**

130 **Sample**

131 The Irish Longitudinal Study on Ageing (TILDA) includes 8175 participants representative of  
132 the community living population aged  $\geq 50$  in Ireland. Households were selected in  
133 geographic clusters from a list of all residential addresses in Ireland. Each selected  
134 household was visited by an interviewer and any resident aged  $\geq 50$  as well as their spouse  
135 or partner were invited to participate. The household response rate was 62.0%. Each  
136 participant provided written informed consent. Those with severe cognitive impairment  
137 preventing meaningful consent were not included in the study. Approval for the study was  
138 obtained from the Trinity College Faculty of Health Sciences Research Ethics Committee.

139

140 Participants underwent a structured interview in their homes covering their health, lifestyle,  
141 social and financial circumstances. 5035 participants agreed to attend for a comprehensive  
142 health center assessment. The sampling procedure and health assessment have been  
143 described in detail previously.<sup>15</sup> Measures specific to the current analysis are detailed  
144 below.

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146 **Frailty**

147 Frailty was assessed using an adaptation of the frailty phenotype.<sup>3</sup> The detailed methods  
148 used are reported elsewhere.<sup>16</sup> Briefly, the criteria were:

149 *Slowness*: The sex specific slowest 20% gait speed from participants aged  $\geq 65$  stratified by  
150 height, based on 16ft walk time. Cut-points were 109.7cm/s for men shorter than 173cm

151 and 116.7cm/s for men taller than 173cm. For women, they were 100.7cm/s for those  
152 shorter than 159cm and 108.4cm/s for those taller than 159cm.

153 *Weakness:* The sex specific lowest 20% grip strength from participants aged  $\geq 65$  stratified by  
154 body mass index (BMI). Cut-points were 20.5kg for men with BMI<24, 21.5kg for men with  
155 BMI of 24-26, and 23kg for men with BMI >26. For women, they were 11.5kg for those with  
156 BMI<23 and 13kg for those with BMI>23

157 *Low Activity:* The sex specific lowest 20% energy expenditure from participants aged  $\geq 65$ ,  
158 based on the International Physical Activity Questionnaire (IPAQ). Cut-points were <868  
159 kcal/week for men and <309 kcal/week for women.

160 *Exhaustion:* Responding 'sometimes' or 'often' to the Centre for Epidemiological Studies  
161 Depression scale (CES-D) items "I could not get going" or "I felt that everything I did was an  
162 effort"

163 *Weight loss:* Self-reporting unintentionally losing  $\geq 10$ lbs in weight in the last year.

#### 164 **Active stand protocol**

165 Participants underwent a lying-to-standing orthostatic test (active stand) with non-invasive  
166 continuous beat-to-beat BP monitoring using digital photoplethysmography (Finometer®  
167 MIDI device, Finapres Medical Systems BV, Amsterdam, The Netherlands,  
168 www.finapres.com). After ten minutes' supine rest participants were asked to stand in a  
169 timely manner (<5 seconds) and were aided by a research nurse when necessary. After  
170 standing, SBP, DBP and heart rate were monitored for three minutes of quiet standing. The  
171 instrument calibration, data processing and feature extraction for this test have been  
172 described in detail previously.<sup>12, 17, 18</sup>

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174 For analysis, beat-to-beat values were averaged according to the 5-second averages method  
175 to filter any noise.<sup>19</sup> Features were then extracted from each record. The algorithm captures  
176 BP and heart rate values at 10-second intervals up to 110 seconds post stand using the 5-  
177 second averages for each time-point. In addition, the lowest BP values (nadirs) and highest  
178 heart rate (maximum) are recorded. Baseline was defined as the mean value from 60-30  
179 seconds prior to standing. From this data additional parameters were calculated, specifically  
180 the percentage of baseline recovered at each time-point and the maximum change (delta) in  
181 BP and heart rate during standing.

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### 183 **Other measures**

184 Height and weight were measured using standard procedures and BMI defined as weight (kg)  
185 divided by height<sup>2</sup> (m). Participants reported doctor diagnoses of any cardiovascular  
186 conditions and gave a list of medications. Participants were also asked about health behaviors  
187 including smoking. Depressive symptoms were assessed using the 20-item CES-D,<sup>20</sup> the two  
188 items used in the frailty definition were excluded from analyses.

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### 190 **Statistical Analysis**

191 Statistical analyses were performed in Stata version 14.2. Differences across frailty groups  
192 were assessed using Analysis of Variance (ANOVA) for normally distributed continuous  
193 variables, Kruskal-Wallis tests for non-normally distributed variables and Chi-squared tests  
194 for categorical variables.

195 Linear mixed effects models (Stata's 'mixed' command) with a participant level random  
196 intercept were used to model the recovery in BP or heart rate from 10-110 seconds post  
197 stand, comparable to modelling change over time in a longitudinal analysis.<sup>21, 22</sup> The primary  
198 outcome measure was the percentage of BP or heart rate recovered over the time standing.  
199 Residual variance across time was modelled using an autoregressive correlation matrix with  
200 a lag of 1 to account for stronger correlations between closer together time-points.

201 Conceptually, the recovery of BP and heart rate can be broken down into an initial rapid  
202 recovery phase followed by a stabilisation and 'levelling off' towards the baseline.  
203 Consequently, we parameterised time using linear splines with knots at 20 and 30 seconds  
204 with the slopes between these knots representing the different phases of the stand (10s-  
205 20s, 20s-30s, 30s-110s).<sup>21</sup> These re-parameterized time variables were included in the  
206 models as fixed effects.

207 Main effects and interactions with the time variables were included for all predictors. The  
208 interaction term between frailty and time represents the effect of frailty on the *rate of*  
209 *recovery* with time in each period, that is to what extent frailty determines the slope of  
210 recovery over that time. To aid interpretation we additionally present conditional mean  
211 responses during the stand, ie the expected values of BP or heart rate recovery (% of  
212 baseline) across frailty groups over time holding all covariates constant at their means. The  
213 basic models included age (as linear and quadratic terms to account for the potential non-  
214 linear relationship) and sex. The full models additionally included fixed between-patient  
215 effects for BMI (linear and quadratic), smoking, antihypertensive (ATC codes C02 and C07)  
216 and antidepressant medications, depressive symptoms and self-reported cardiovascular  
217 conditions; hypertension, diabetes, stroke, heart attack, angina and heart murmur.

218 Relationships with the individual frailty criteria were modelled using the same approach.

219 The full model outputs are provided in supplemental appendix tables SA1-7.

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236 **Results**

237 Data on frailty and orthostatic BP responses were available for 4334 participants from the  
238 health center sample, with a mean (SD) age of 61.6 (8.2) years (Table 1). 2327 (53.7%) were  
239 female, 2674 (61.7%) had  $\geq 1$  cardiovascular conditions and 638 (14.7%) were current  
240 smokers (Table 1). 93 (2.2%) participants were frail and 1366 (31.51 %) prefrail. Frailer  
241 participants had higher BMI and depressive symptoms and levels of current smoking and  
242 medication use (all  $p < 0.001$ ).

243 The overall resting mean (SD) SBP was 136.2 (22.3) mmHg, DBP 73.3 (11.2) mmHg and heart  
244 rate 65.2 (10.1) beats per minute (bpm) (Table 1). There was a trend towards higher  
245 baseline SBP across the frailty groups, while baseline DBP was lower (Table 1). Baseline  
246 heart rate was higher in frail participants; 67.6 (10.3), compared to 64.7 (9.7) in robust ( $p$   
247  $< 0.001$ ). The maximum drop in SBP and DBP was similar across groups, while the maximum  
248 increase in heart rate was smaller in frail participants, 18.8 (8.2) compared to 20.1 (8.7)  
249 ( $p = 0.011$ ) in robust.

250 Table 1 shows the coefficients for the relationships between frailty category and rate of  
251 recovery for each phase of the stand for % baseline BP or heart rate recovered. Conditional  
252 values from the models are shown in Figure 1. After controlling for age and sex, frailty was  
253 associated a slower recovery rate between 10-20 seconds after standing in both SBP (-  
254 4.12%/10s 95%CI=-5.53, -2.72 in frail compared to robust; -0.99 (-1.37,-0.60) for prefrail)  
255 and DBP (frail: -5.26 (-6.87,-3.65); prefrail: -1.80 (-2.24,-1.36)). Correspondingly, frailty was  
256 associated with deficits of approximately 3-4% in SBP and DBP over the following 40  
257 seconds (20-60 seconds post standing, Figure 1 & Table S1). DBP was actually higher relative  
258 to baseline at 10 seconds suggestive of a more gradual pattern of drop and recovery (Fig 1).

259 There was little difference in the rate of recovery between 20-30 seconds, but frailty was  
260 associated with a steeper slope from 30-110 seconds for SBP recovery, as BP continued to  
261 recover over this time in frailer people. The general patterns of results were similar using  
262 the BP values in mmHG at each time point, rather than the percentage of baseline as the  
263 outcome variables (Supplemental Table 2 and Figure 1). The models also suggested residual  
264 variance was higher in frailer people, especially for SBP (Appendix tables 1 & 2).

265 Further adjustment for BMI, smoking, depressive symptoms, cardiovascular conditions and  
266 medications partially reduced the differences in the initial recovery slopes in SBP and DBP  
267 (Table 2). Although much of the relationship remained, the associated deficits in SBP and  
268 DBP were reduced to 1-2% lower in frail compared to robust (Figure 1).

269 Heart rate was higher throughout standing in the frail and prefrail groups compared to  
270 robust reflecting the higher baseline (Supplemental Fig 1). In the main analysis, heart rate  
271 effectively mirrored the BP responses with a slower rate of decrease in heart rate (between  
272 10-20 seconds) (Table 2). Heart rate was then slightly higher relative to baseline at 20  
273 seconds with the difference between groups diminishing over the rest of the stand. As with  
274 BP further adjustment partially attenuated the slope from 10 seconds, although differences  
275 between groups at 20 seconds remained similar as adjustment also reduced the trend  
276 towards relatively lower peak heart rate at 10 seconds.

277 After adjustment for all covariates and the other frailty criteria, slow gait speed was  
278 associated with slower rate of recovery in BP and heart rate between 10-20 seconds (Table  
279 3), and with deficits in SBP and to a lesser extent DBP throughout the following 40 seconds  
280 post standing (Figure 2). Slow gait was also associated with lower heart rate at 10s and  
281 higher values at 20 seconds post stand. Weight loss was associated with mild deficits in DBP

282 recovery. Exhaustion was associated with reduced recovery rate for SBP and heart rate, but  
283 not clearly with deficits at any time point (Table 3).

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300 **Discussion**

301 Frailty was associated with slower BP and heart rate recovery following standing in this  
302 sample of community dwelling middle-aged to older adults. In general less than half the  
303 effect was explained by adjustment for health behaviours, morbidities and medication use.  
304 When considered separately only slow gait speed was consistently related to impaired SBP  
305 and to a lesser extent DBP and heart rate responses independently of cardiovascular  
306 morbidities, medication use and the other frailty criteria.

307 Frailty has been associated with (sub)clinical cardiovascular disease and with impaired  
308 autonomic cardiovascular control.<sup>11, 23</sup> However, previous analyses from TILDA and the  
309 Canadian Study of Health and Aging have not shown clear relationships between OH and  
310 physical frailty.<sup>8, 9</sup> The conventional OH measurement used in these studies is based on  
311 discrete measurements which do not detect the early transient BP responses. An earlier  
312 beat-to-beat monitoring study found univariate trends towards impaired SBP recovery in  
313 frailer participants in a convenience sample of older adults.<sup>14</sup> The present study extends  
314 these findings using more sophisticated statistical methods to better characterise BP  
315 behaviour within a larger sample drawn from a population representative survey.

316 An increasingly detailed theoretical framework links frailty or resilience to an individual's  
317 capacity to resist stressors.<sup>1, 24, 25, 26</sup> However, direct support is lacking, with the best  
318 evidence so far coming from impaired response to Oral Glucose Tolerance test in frail older  
319 women.<sup>27</sup> The reduced BP recovery rate associated with frailty in this study provides some  
320 further support for this hypothesis.

321 The general pattern in frailer participants was a blunted early response in both BP and heart  
322 rate consistent with poorer autonomic compensation mechanisms following the stress of  
323 standing, and associated with deficits of 3-4% in BP over 30-40 seconds during the 1<sup>st</sup>  
324 minute post stand. It is worth noting the relatively modest size of these differences across  
325 groups and their functional significance is not yet clear. The small mean deficits may also  
326 reflect the relatively large variance across frail participants.

327 Recent findings of excess mortality in older falls patients experiencing impaired early BP  
328 recovery post standing, suggest transient deficits or later stabilisation of BP may be a  
329 marker of underlying physiological impairment.<sup>13</sup> Similarly, elevated resting heart rate is  
330 associated with increased mortality rates and may reflect low physical fitness and subclinical  
331 cardiovascular disease.<sup>28, 29</sup> Previous data from TILDA outlined an association between  
332 slower orthostatic heart rate recovery and increased 4-year mortality risk.<sup>22</sup> These  
333 hemodynamic differences could also contribute directly to adverse outcomes like falls in  
334 frail older adults. Analyses from TILDA found increased 2-year falls risk associated with  
335 delayed or incomplete BP recovery.<sup>30</sup> In another study, greater drops in BP and higher  
336 resting heart rate were associated with increased risk of low energy fractures (suggestive of  
337 injurious falls) over 25 years.<sup>31</sup>

338 Adjustment for morbidities, health behaviours and medications only partially attenuated the  
339 differences in BP recovery rates, although deficits between frail and robust groups were  
340 reduced to 1-2%. The interpretation of this is unclear, it may be that impaired BP responses  
341 reflect both an intrinsic physiological frailty and the burden of associated health deficits.<sup>32</sup>

342 Of the 5 frailty criteria, only slow gait speed was consistently related to poorer BP and heart  
343 rate recovery in fully adjusted models. Slower gait is strongly related to subsequent health

344 outcomes in older adults and has been suggested as a measure of frailty in its own right.<sup>33, 34</sup>  
345 The lack of consistent association with the other criteria indirectly suggests slow gait may  
346 actually be a more useful measure of physiological frailty than the frailty phenotype  
347 composite.

348 There may also be specific mechanisms linking slower gait speed and impaired orthostatic  
349 BP responses. OH has been associated with poorer peripheral motor nerve function in older  
350 adults.<sup>35</sup> It has also been associated with increased burden of White Matter Hyperintensities  
351 (WMH) on Magnetic Resonance Imaging scans, thought to reflect cerebral small vessel  
352 disease, in late life depression.<sup>36</sup> A number of cross-sectional and longitudinal studies have  
353 linked these brain changes to mobility decline.<sup>37-40</sup>

354 The immediate clinical implications of these findings are that poorer orthostatic BP  
355 regulation should be considered as a possible cause of falls in frailer older adults before  
356 instigating more intensive BP control as in the SPRINT trial.<sup>41</sup> More broadly they suggest a  
357 single mobility test provides sufficient information on physiological frailty to aid clinical  
358 decision making. Work from TILDA increasingly indicates the rate of recovery in BP and  
359 heart rate to be more informative than the size of initial drops in older adults.<sup>22, 30</sup> And, if  
360 validated further, non-invasive measures of BP homeostasis could provide a quick and  
361 effective means to assess physiological reserve.

362 Strengths of this study include the high quality assessments of frailty and orthostatic  
363 responses within this large sample and the breadth of data collected on potential  
364 confounding variables. The mixed modelling approach used provides a useful summary of  
365 the BP responses, but further work is needed to more completely model variation in the

366 shape of responses, identify the most meaningful parameters and optimally account for  
367 varying correlations between time-points.

368 The study also has some general limitations. It was not possible to control for factors that  
369 influence BP such as feeding or hydration status, although these factors did not affect BP  
370 behavior in a sub-study.<sup>42</sup> The mean age of the sample was 61.6 years and participants  
371 attending the health assessment were generally healthier than those who declined, limiting  
372 the prevalence of frailty. Despite the large overall sample the relatively small number of frail  
373 participants may have limited statistical power as well as the generalizability of the findings  
374 within the relatively young Irish population. The comparative healthiness of the sample may  
375 partially explain the modest size of effects. The cross-sectional design precludes  
376 determination of the causal direction of relationships. Findings were based on almost  
377 exclusively Caucasian Irish adults and should be extrapolated beyond this setting with care.

378 In summary, physical frailty, and especially slow gait speed, is associated with impairments  
379 in early orthostatic BP and heart rate recovery in older adults. Future studies to further  
380 establish the utility of orthostatic hemodynamics as measures of physiological frailty and  
381 their relationship to mobility decline are warranted.

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394 Development Awards in Aging Research for the Island of Ireland. Researchers interested in  
395 using TILDA data may access the data for free from the following sites:

- 396 • Irish Social Science Data Archive (ISSDA) at University College Dublin  
397 [www.ucd.ie/issda/data/tilda/](http://www.ucd.ie/issda/data/tilda/)
  
- 398 • Interuniversity Consortium for Political and Social Research (ICPSR) at the University  
399 of Michigan <http://www.icpsr.umich.edu/icpsrweb/ICPSR/studies/34315>

400

401 **Author Contributions**

402 MOC performed the analysis and drafted the manuscript. GS, CF, contributed to data  
403 analysis. CF, CWF, RAK contributed to data acquisition. MOC, GS, CF, RRO, CWF, RAK  
404 conceived the study, contributed to interpretation of data and critical revision of article for  
405 important intellectual content and gave final approval for submission.

406

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408 **Conflict of Interest: The authors declare no conflict of interest.**

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|--|-------------------|----|----------------|----|----------------|----|-----------------|----|
|  | Yes               | No | Yes            | No | Yes            | No | Yes             | No |
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| <b>Personal Relationship</b>                   |                   |    |                |    |                |    |                 |    |

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|--|--|---|--|---|--|---|--|---|

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| Elements of<br>Financial/Personal<br>Conflicts | *Author 1<br>CWF |    | Author 2<br>RAK |    | Author 3 |    | Author 4 |    |
|--|------------------|----|-----------------|----|----------|----|----------|----|
|  | Yes              | No | Yes             | No | Yes      | No | Yes      | No |
| <b>Employment or<br/>Affiliation</b>           |                  |    |                 |    |          |    |          |    |
|  |                  | X  |                 | X  |          |    |          |    |
| <b>Grants/Funds</b>                            |                  |    |                 |    |          |    |          |    |
|  |                  | X  |                 | X  |          |    |          |    |
| <b>Honoraria</b>                               |                  |    |                 |    |          |    |          |    |
|  |                  | X  |                 | X  |          |    |          |    |
| <b>Speaker Forum</b>                           |                  |    |                 |    |          |    |          |    |
|  |                  | X  |                 | X  |          |    |          |    |
| <b>Consultant</b>                              |                  |    |                 |    |          |    |          |    |
|  |                  | X  |                 | X  |          |    |          |    |
| <b>Stocks</b>                                  |                  |    |                 |    |          |    |          |    |
|  |                  | X  |                 | X  |          |    |          |    |
| <b>Royalties</b>                               |                  |    |                 |    |          |    |          |    |
|  |                  | X  |                 | X  |          |    |          |    |
| <b>Expert Testimony</b>                        |                  |    |                 |    |          |    |          |    |
|  |                  | X  |                 | X  |          |    |          |    |
| <b>Board Member</b>                            |                  |    |                 |    |          |    |          |    |
|  |                  | X  |                 | X  |          |    |          |    |
| <b>Patents</b>                                 |                  |    |                 |    |          |    |          |    |
|  |                  | X  |                 | X  |          |    |          |    |

| Personal Relationship |  |   |  |   |  |  |  |  |
|-----------------------|--|---|--|---|--|--|--|--|
|                       |  | X |  | X |  |  |  |  |

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## **Supplemental data titles**

Table S1: Conditional differences in blood pressure or heart rate recovery compared to robust category (% baseline)

Table S2: Model parameters for blood pressure and heart rate recovery following active standing (mmHg or heart rate)

Table S3: Conditional differences in blood pressure or heart rate recovery compared to robust category in (mmHg or heart rate)

Figure S1: Conditional mean blood pressure and heart rate responses across frailty categories (mmHg or heart rate)

Table SA1: Mixed effects models for SBP recovery (% baseline)

Table SA2: Mixed effects models for DBP recovery (% baseline)

Table SA3: Mixed effects models for heart rate recovery (% baseline)

Table SA4: Mixed effects models for SBP recovery (mmHg)

Table SA5: Mixed effects models for DBP recovery (mmHg)

Table SA6: Mixed effects models for heart rate recovery (heart rate)

Table SA7: Mixed effects models for BP & heart rate recovery by frailty criteria (% baseline)

## Graphics

**Table 1: Participant characteristics**

|                                    | Overall<br>n=4334 | Robust<br>n=2875 | Prefrail<br>n=1366 | Frail<br>n=93 | P                   |
|------------------------------------|-------------------|------------------|--------------------|---------------|---------------------|
| Age (mean (SD))                    | 61.6 (8.2)        | 60.5 (7.6)       | 63.4 (8.9)         | 68.0 (11.2)   | <0.001 <sup>a</sup> |
| Female (count (%))                 | 2327 (53.7)       | 1537 (53.5)      | 738 (54.0)         | 52 (55.9)     | 0.86 <sup>b</sup>   |
| BMI (mean (SD))                    | 28.5 (4.9)        | 28.2 (4.7)       | 29.1 (5.0)         | 29.3 (7.0)    | <0.001 <sup>a</sup> |
| Depressive symptoms (median (IQR)) | 3 (1 - 7)         | 3 (0 - 5)        | 5 (1 - 10)         | 10 (5 - 20)   | <0.001 <sup>c</sup> |
| Current smoker (count (%))         | 638 (14.7)        | 379 (13.2)       | 234 (17.1)         | 25 (26.9)     | <0.001 <sup>a</sup> |
| Any CVD condition (count (%))      | 2674 (61.7)       | 1678 (58.4)      | 924 (67.6)         | 72 (77.4)     | <0.001 <sup>a</sup> |
| On antihypertensives (count (%))   | 568 (13.2)        | 316 (11.0)       | 236 (17.4)         | 16 (17.8)     | <0.001 <sup>a</sup> |
| On antidepressants (count (%))     | 256 (5.9)         | 108 (3.8)        | 125 (9.2)          | 23 (25.6)     | <0.001 <sup>a</sup> |
| Baseline systolic BP (mean (SD))   | 136.2 (22.3)      | 135.8 (21.7)     | 136.9 (23.2)       | 138.6 (25.5)  | 0.15 <sup>a</sup>   |
| Max Δ systolic BP (mean (SD))      | -39.3 (17.9)      | -39.0 (17.4)     | -39.8 (18.7)       | -41.6 (19.3)  | 0.17 <sup>a</sup>   |
| Baseline diastolic BP (mean (SD))  | 73.3 (11.2)       | 73.6 (11.0)      | 72.7 (11.6)        | 71.4 (11.2)   | 0.016 <sup>a</sup>  |
| Max Δ diastolic BP (mean (SD))     | -25.8 (10.3)      | -25.9 (10.1)     | -25.8 (10.8)       | -25.0 (10.8)  | 0.74 <sup>a</sup>   |
| Baseline heart rate (mean (SD))    | 65.2 (10.1)       | 64.7 (9.7)       | 66.1 (10.7)        | 67.6 (10.3)   | <0.001 <sup>a</sup> |
| Max Δ heart rate (mean (SD))       | 19.8 (8.9)        | 20.1 (8.7)       | 19.3 (9.2)         | 18.8 (8.2)    | 0.011 <sup>a</sup>  |

<sup>a</sup>ANOVA <sup>b</sup>Chi-square <sup>c</sup>Kruskal-Wallis

**Table 2: Model parameters for blood pressure and heart rate recovery following active standing (% recovery)**

|                     | Frailty*Time (rate of recovery) |                        |                    |                    |
|---------------------|---------------------------------|------------------------|--------------------|--------------------|
|                     | Intercept (10s difference)      | 10-20s                 | 20-30s             | 30-110s            |
| <b>Systolic BP</b>  |                                 |                        |                    |                    |
| Model 1             |                                 |                        |                    |                    |
| Prefrail            | 0.39 [-0.41,1.20]               | -0.99 [-1.37,-0.60]*** | 0.01 [-0.38,0.39]  | 0.15 [0.06,0.25]** |
| Frail               | 0.29 [-2.58,3.17]               | -4.12 [-5.53,-2.72]*** | -0.25 [-1.65,1.15] | 0.46 [0.10,0.82]*  |
| Model 2             |                                 |                        |                    |                    |
| Prefrail            | 0.44 [-0.40,1.28]               | -0.88 [-1.29,-0.47]*** | 0.07 [-0.34,0.48]  | 0.10 [-0.00,0.20]  |
| Frail               | 1.07 [-1.97,4.10]               | -2.71 [-4.21,-1.21]*** | -0.29 [-1.79,1.21] | 0.27 [-0.12,0.66]  |
| <b>Diastolic BP</b> |                                 |                        |                    |                    |
| Model 1             |                                 |                        |                    |                    |
| Prefrail            | 0.80 [-0.01,1.61]               | -1.80 [-2.24,-1.36]*** | -0.18 [-0.62,0.26] | 0.15 [0.05,0.24]** |
| Frail               | 2.77 [0.10,5.44]*               | -5.26 [-6.87,-3.65]*** | -1.17 [-2.77,0.42] | 0.25 [-0.07,0.58]  |
| Model 2             |                                 |                        |                    |                    |
| Prefrail            | 0.55 [-0.31,1.40]               | -1.39 [-1.86,-0.92]*** | 0.07 [-0.40,0.53]  | 0.10 [-0.00,0.20]  |
| Frail               | 2.59 [-0.27,5.45]               | -3.44 [-5.16,-1.71]*** | -0.76 [-2.47,0.95] | 0.09 [-0.26,0.44]  |
| <b>Heart rate</b>   |                                 |                        |                    |                    |
| Model 1             |                                 |                        |                    |                    |
| Prefrail            | -1.26 [-1.93,-0.59]***          | 1.74 [1.36,2.13]***    | -0.03 [-0.41,0.35] | -0.06 [-0.14,0.01] |
| Frail               | -2.02 [-4.20,0.16]              | 4.92 [3.73,6.11]***    | -1.10 [-2.29,0.08] | -0.24 [-0.49,0.01] |
| Model 2             |                                 |                        |                    |                    |
| Prefrail            | -0.51 [-1.22,0.19]              | 1.22 [0.81,1.62]***    | 0.07 [-0.33,0.47]  | -0.03 [-0.11,0.05] |
| Frail               | 0.70 [-1.64,3.03]               | 2.41 [1.12,3.70]***    | -1.12 [-2.40,0.16] | -0.17 [-0.45,0.10] |

Parameters are estimated from mixed effects models with linear splines. Interaction coefficients represent the difference in slopes or rate of recovery in blood pressure or heart rate at each stage of the active stand. Model 1: Age and sex, Model 2: Age, sex, BMI, smoking, depressive symptoms, self-reported CVD conditions, medication use \*P<0.05, \*\*P<0.01, \*\*\*P<0.001

**Table 3: Model parameters for the relationships between frailty criteria and blood pressure and heart rate recovery (% baseline)**

|                     | Intercept (10s difference) | Frailty*Time (rate of recovery) |                      |                    |
|---------------------|----------------------------|---------------------------------|----------------------|--------------------|
|                     |                            | 10-20s                          | 20-30s               | 30-110s            |
| <b>Systolic BP</b>  |                            |                                 |                      |                    |
| Slowness            | -0.72 [-2.12,0.68]         | -2.33 [-3.02,-1.64]***          | 0.96 [0.27,1.65]**   | 0.22 [0.06,0.39]** |
| Activity            | 0.69 [-0.36,1.73]          | -0.48 [-0.99,0.04]              | -0.45 [-0.96,0.06]   | 0.06 [-0.06,0.18]  |
| Grip                | 0.09 [-1.23,1.40]          | -0.41 [-1.05,0.24]              | 0.56 [-0.09,1.20]    | 0.05 [-0.11,0.20]  |
| Exhaustion          | 1.12 [-0.38,2.63]          | -0.76 [-1.50,-0.02]*            | -0.89 [-1.63,-0.16]* | 0.11 [-0.07,0.29]  |
| Weight loss         | 0.24 [-1.29,1.77]          | -0.61 [-1.37,0.14]              | -0.74 [-1.49,0.01]   | 0.03 [-0.15,0.21]  |
| <b>Diastolic BP</b> |                            |                                 |                      |                    |
| Slowness            | 1.89 [0.45,3.32]**         | -3.82 [-4.59,-3.04]***          | 0.70 [-0.07,1.47]    | 0.11 [-0.05,0.27]  |
| Activity            | 0.64 [-0.43,1.71]          | -0.56 [-1.14,0.02]              | -0.64 [-1.21,-0.06]* | 0.05 [-0.07,0.17]  |
| Grip                | -0.22 [-1.57,1.12]         | -0.26 [-0.98,0.47]              | 0.66 [-0.07,1.38]    | 0.01 [-0.15,0.16]  |
| Exhaustion          | 0.73 [-0.81,2.27]          | -0.62 [-1.45,0.22]              | -0.70 [-1.53,0.13]   | 0.12 [-0.05,0.30]  |
| Weight loss         | 0.30 [-1.27,1.87]          | -1.11 [-1.96,-0.26]*            | -0.92 [-1.76,-0.07]* | 0.05 [-0.13,0.23]  |
| <b>Heart rate</b>   |                            |                                 |                      |                    |
| Slowness            | -1.76 [-2.96,-0.55]**      | 3.26 [2.57,3.96]***             | -0.25 [-0.94,0.43]   | -0.10 [-0.23,0.04] |
| Activity            | 0.26 [-0.63,1.16]          | 0.21 [-0.30,0.73]               | 0.04 [-0.47,0.55]    | 0.02 [-0.08,0.12]  |
| Grip                | 0.29 [-0.84,1.41]          | 0.53 [-0.12,1.18]               | -0.39 [-1.03,0.26]   | -0.02 [-0.15,0.11] |
| Exhaustion          | -0.64 [-1.93,0.65]         | 1.20 [0.46,1.95]**              | 0.47 [-0.26,1.21]    | -0.09 [-0.24,0.06] |
| Weight loss         | 0.16 [-1.15,1.47]          | 0.05 [-0.71,0.80]               | 0.15 [-0.60,0.90]    | -0.01 [-0.16,0.14] |

Parameters are estimated from mixed effects models with linear splines. Interaction coefficients represent the difference in slopes or rate of recovery in blood pressure or heart rate at each stage of the active stand. Models include age, sex, BMI, smoking, depressive symptoms, self-reported CVD conditions, medication use. \*P<0.05, \*\*P<0.01, \*\*\*P<0.001

**Figure legends:**

**Figure 1: Conditional mean blood pressure and heart rate responses across frailty categories (% baseline)**

Data are conditional means and 95% confidence intervals estimated from mixed effects models. Model 1: Age and sex; Model 2: age, sex, BMI, smoking, antihypertensive and antidepressant medication use, depressive symptoms and CVD conditions.

**Figure 2: Conditional differences in blood pressure and heart rate recovery according to the presence of each frailty criterion (% baseline)**

Data are conditional differences and 95% confidence intervals relative to the reference not having the criterion estimated from mixed models. All models include age, sex, BMI, smoking, antihypertensive and antidepressant medication use, depressive symptoms and CVD conditions, and are mutually adjusted for the presence of the other frailty criteria.