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

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Manuscripts

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

2   **from TILDA**

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18   Abbreviated title: Frailty and Orthostatic Blood Pressure

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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 BP and heart rate recovery and frailty in an older

40   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 blood pressure (BP) responses during active

46   standing were captured by Finometer®. Frailty was assessed using the Cardiovascular Health

47   Study criteria. Linear mixed models (random intercept) with piecewise splines were used to

48   model 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

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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 was 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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Introduction

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

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

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

Discrete BP measurements capture only a fraction of the full hemodynamic responses. Studies using continuous BP monitoring suggest aging is characterised by a gradual slowing of initial BP recovery post-standing, indicative of declining BP homeostatic function.[12] Recent data has linked impairments in early BP recovery to mortality in older falls clinic

109   patients.[13] Similarly, pilot data from a convenience sample of older Irish adults suggested

110   possible relationships between orthostatic hemodynamics and frailty.[14]

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.[14]

116   This study aimed to characterise the BP and HR responses to orthostasis across levels of

117   frailty within a large population sample of middle-aged to older adults and to assess the role

118   of health conditions and medications in these relationships. We further aimed to explore

119   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 ≥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 ≥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.

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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.[15] 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.[3] The detailed methods

148   used are reported elsewhere.[16] Briefly, the criteria were:

149   *Slowness:* The sex specific slowest 20% gait speed from participants aged ≥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 ≥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 ≥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 ≥10lbs 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 HR 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.[12, 17, 18]

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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.[19] Features were then extracted from each record. The algorithm captures

176   BP and HR values at 10-second intervals up to 110 seconds post stand using the 5-second

177   averages for each time-point. In addition, the lowest BP values (nadirs) and highest HR

178   (maximum) are recorded. Baseline was defined as the mean value from 60-30 seconds prior

179   to standing. From this data additional parameters were calculated, specifically the

180   percentage of baseline recovered at each time-point and the maximum change (delta) in BP

181   and HR during standing.

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183   **Other measures**

184   Height and weight were measured using standard procedures and BMI defined as weight

185   (kg) divided by height^2 (m). Participants reported doctor diagnoses of any cardiovascular

186   conditions and gave a list of medications. Participants were also asked about health

187   behaviors including smoking. Depressive symptoms were assessed using the 20-item CES-

188   D,[20] the two 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, Kruskil-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.[21, 22] 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).[21] 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 HR recovery (% of baseline)

212 across frailty groups over time holding all covariates constant at their means. The basic

213 models included age (as linear and quadratic terms to account for the potential non-linear

214 relationship) and sex. The full models additionally included fixed between-patient effects for

215 BMI (linear and quadratic), smoking, antihypertensive (ATC codes C02 and C07) and

216 antidepressant medications, depressive symptoms and self-reported cardiovascular

217 conditions; hypertension, diabetes, stroke, heart attack, angina and heart murmur.

218   <mark>Relationships with the individual frailty criteria were modelled using the same approach.</mark>

219   <mark>The full model outputs are provided in supplemental appendix tables 1-7.</mark>

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Results

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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 ≥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 HR

244 65.2 (10.1) beats per minute (bpm) (Table 1). There was a trend towards higher baseline SBP

245 across the frailty groups, while baseline DBP was lower (Table 1). Baseline HR was higher in

246 frail participants; 67.6 (10.3), compared to 64.7 (9.7) in robust (p <0.001). The maximum

247 drop in SBP and DBP was similar across groups, while the maximum increase in HR was

248 smaller in frail participants, 18.8 (8.2) compared to 20.1 (8.7) (p=0.011) in robust.

249 Table 1 shows the coefficients for the relationships between frailty category and rate of

250 recovery for each phase of the stand for % baseline BP or heart rate recovered. Conditional

251 values from the models are shown in Figure 1. After controlling for age and sex, frailty was

252 associated a slower recovery rate between 10-20 seconds after standing in both SBP (-

253 4.12%/sec 95%CI=-5.53, -2.72 in frail compared to robust; -0.99 (-1.37,-0.60) for prefrail)

254 and DBP (frail: -5.26 (-6.87,-3.65); prefrail: -1.80 (-2.24,-1.36)). Correspondingly, frailty was

255 associated with deficits of approximately 3-4% in SBP and DBP over the following 40

256 seconds (20-60 seconds post standing, Figure 1 & Table S1). DBP was actually higher at 10

257 seconds suggestive of a more gradual pattern of drop and recovery (Fig 1). There was little

258 difference in the rate of recovery between 20-30 seconds, but frailty was associated with a

259   steeper slope from 30-110 seconds for SBP recovery, as BP continued to recover over this

260   time in frailer people. The general patterns of results were similar using the BP values in

261   mmHG at each time point, rather than the percentage of baseline as the outcome variables

262   (Supplemental Table 2 and Figure 1). The models also suggested residual variance was

263   higher in frailer people, especially for SBP (Appendix tables 1 & 2).

264   Further adjustment for BMI, smoking, depressive symptoms, cardiovascular conditions and

265   medications partially reduced the differences in the initial recovery slopes in SBP and DBP

266   (Table 2). Although much of the relationship remained, the associated deficits in SBP and

267   DBP were reduced to 1-2% lower in frail compared to robust (Figure 1).

268   HR was higher throughout standing in the frail and prefrail groups compared to robust

269   reflecting the higher baseline (Supplemental Fig 1). In the main analysis, heart rate

270   effectively mirrored the BP responses with a slower rate of decrease in heart rate (between

271   10-20 seconds) (Table 2). Heart rate was then slightly higher relative to baseline at 20

272   seconds with the difference between groups diminishing over the rest of the stand. As with

273   BP further adjustment partially attenuated the slope from 10 seconds, although differences

274   between groups at 20 seconds remained similar as adjustment also reduced the lower peak

275   heart rate at 10 seconds.

276   After adjustment for all covariates and the other frailty criteria, slow gait speed was

277   associated with slower rate of recovery in BP and heart rate between 10-20 seconds (Table

278   3), and with deficits in SBP and to a lesser extent DBP throughout the following 40 seconds

279   post standing (Figure 2). Slow gait was also associated with lower peak heart rate and higher

280   values at 20 seconds post stand. Weight loss was associated with mild deficits in DBP

281   recovery. Exhaustion was associated with reduced recovery rate for SBP and heart rate, but

282   not clearly with deficits at any time point (Table 3).

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Discussion

300   Frailty was associated with <mark>slower BP and heart rate recovery following standing</mark> in this

301   sample of community dwelling middle-aged to older adults. In general less than half the

302   effect was explained by adjustment for health behaviours, morbidities and medication use.

303   <mark>When considered separately only slow gait speed was consistently related to impaired SBP</mark>

304   <mark>and to a lesser extent DBP and HR responses independently of cardiovascular morbidities,</mark>

305   <mark>medication use and the other frailty criteria.</mark>

306   Frailty has been associated with (sub)clinical cardiovascular disease and with impaired

307   autonomic cardiovascular control.[11, 23] However, previous analyses from TILDA and the

308   Canadian Study of Health and Aging have not shown clear relationships between OH and

309   physical frailty.[8, 9] The conventional OH measurement used in these studies is based on

310   discrete measurements which do not detect the early transient BP responses. An earlier

311   beat-to-beat monitoring study found univariate trends towards impaired SBP recovery in

312   frailer participants in a convenience sample of older adults.[14] The present study extends

313   these findings using more sophisticated statistical methods to better characterise BP

314   behaviour within a larger sample drawn from a population representative survey.

315   An increasingly detailed theoretical framework links frailty or resilience to an individual's

316   capacity to resist stressors.[1, 24, 25,26] However, direct support is lacking, with the best

317   evidence so far coming from impaired response to Oral Glucose Tolerance test in frail older

318   women.[27] <mark>The reduced BP recovery rate associated with frailty in this study provides some</mark>

319   <mark>further support for this hypothesis.</mark>

320   The general pattern in frailer participants was a blunted early response in both BP and heart

321   rate consistent with poorer autonomic compensation mechanisms following the stress of

322   standing, and associated with deficits of 3-4% in BP over 30-40 seconds during the 1st

323   minute post stand. It is worth noting the relatively modest size of these differences across

324   groups and their functional significance is not yet clear. The small mean deficits may also

325   reflect the relatively large variance across frail participants.

326   Recent findings of excess mortality in older falls patients experiencing impaired early BP

327   recovery post standing, suggest transient deficits or later stabilisation of BP may be a

328   marker of underlying physiological impairment.[13] Similarly, elevated resting heart rate is

329   associated with increased mortality rates and may reflect low physical fitness and subclinical

330   cardiovascular disease.[28, 29] Previous data from TILDA outlined an association between

331   slower orthostatic heart rate recovery and increased 4-year mortality risk.[22] These

332   hemodynamic differences could also contribute directly to adverse outcomes like falls in

333   frail older adults. Analyses from TILDA found increased 2-year falls risk associated with

334   delayed or incomplete BP recovery.[30] In another study, greater drops in BP and higher

335   resting heart rate were associated with increased risk of low energy fractures (suggestive of

336   injurious falls) over 25 years.[31]

337   Adjustment for morbidities, health behaviours and medications only partially attenuated the

338   differences in BP recovery rates, although deficits between frail and robust groups were

339   reduced to 1-2%. The interpretation of this is unclear, it may be that impaired BP responses

340   reflect both an intrinsic physiological frailty and the burden of associated health deficits.[32]

341   Of the 5 frailty criteria, only slow gait speed was consistently related to poorer BP and heart

342   rate recovery in fully adjusted models. Slower gait is strongly related to subsequent health

343 outcomes in older adults and has been suggested as a measure of frailty in its own right.[33, 34]

344 The lack of consistent association with the other criteria indirectly suggests slow gait may

345 actually be a more useful measure of physiological frailty than the frailty phenotype

346 composite.

347 There may also be specific mechanisms linking slower gait speed and impaired orthostatic

348 BP responses. OH has been associated with poorer peripheral motor nerve function in older

349 adults.[35] It has also been associated with increased burden of White Matter Hyperintensities

350 (WMH) on Magnetic Resonance Imaging scans, thought to reflect cerebral small vessel

351 disease, in late life depression.[36] A number of cross-sectional and longitudinal studies have

352 linked these brain changes to mobility decline.[37-40]

353 The immediate clinical implications of these findings are that poorer orthostatic BP

354 regulation should be considered as a possible cause of falls in frailer older adults before

355 instigating more intensive BP control as in the SPRINT trial.[41] More broadly they suggest a

356 single mobility test provides sufficient information on physiological frailty to aid clinical

357 decision making. Work from TILDA increasingly indicates the rate of recovery in BP and

358 heart rate to be more informative than the size of initial drops in older adults.[22, 30] And, if

359 validated further, non-invasive measures of BP homeostasis could provide a quick and

360 effective means to assess physiological reserve.

361 Strengths of this study include the high quality assessments of frailty and orthostatic

362 responses within this large sample and the breadth of data collected on potential

363 confounding variables. The mixed modelling approach used provides a useful summary of

364 the BP responses, but further work is needed to more completely model variation in the

365   shape of responses, identify the most meaningful parameters and optimally account for

366   varying correlations between time-points.

367   The study also has some general limitations. It was not possible to control for factors that

368   influence BP such as feeding or hydration status, although these factors did not affect BP

369   behavior in a sub-study.[42] The mean age of the sample was 61.6 years and participants

370   attending the health assessment were generally healthier than those who declined, limiting

371   the prevalence of frailty. Despite the large overall sample the relatively small number of frail

372   participants may have limited statistical power as well as the generalizability of the findings

373   within the relatively young Irish population. The comparative healthiness of the sample may

374   partially explain the modest size of effects. The cross-sectional design precludes

375   determination of the causal direction of relationships. Findings were based on almost

376   exclusively Caucasian Irish adults and should be extrapolated beyond this setting with care.

377   In summary, physical frailty, and especially slow gait speed, is associated with impairments

378   in early orthostatic BP and HR recovery in older adults. Future studies to further establish

379   the utility of orthostatic hemodynamics as measures of physiological frailty and their

380   relationship to mobility decline are warranted.

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400   **Author Contributions**

401   MOC performed the analysis and drafted the manuscript. GS, CF, contributed to data

402   analysis. CF, CWF, RAK contributed to data acquisition. MOC, GS, CF, RRO, CWF, RAK

403   conceived the study, contributed to interpretation of data and critical revision of article for

404   important intellectual content and gave final approval for submission.

405

406   **Sponsor's role:** None

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

Elements of Financial/Personal Conflicts	*Author 1 MO'C		Author 2 GS		Author 3 CF		Author 4 RRO	
	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation								
		X		X		X		X
Grants/Funds								
		X		X		X		X
Honoraria								
		X		X		X		X
Speaker Forum								
		X		X		X		X
Consultant								
		X		X		X		X
Stocks								
		X		X		X		X
Royalties								
		X		X		X		X
Expert Testimony								
		X		X		X		X
Board Member								
		X		X		X		X
Patents								
		X		X		X		X
Personal Relationship								

	Yes	No	Yes	No	Yes	No	Yes	No
		X		X		X		X

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Elements of Financial/Personal Conflicts	*Author 1 CWF		Author 2 RAK		Author 3		Author 4	
	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation								
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Grants/Funds								
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Honoraria								
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Speaker Forum								
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Expert Testimony								
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Board Member								
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Patents								
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Personal Relationship								
		X		X				

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Graphics

Table 1: Participant characteristics

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

[a]ANOVA [b]Chi-square [c]Kruskil-Wallis

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

	Intercept (10s difference)	Frailty*Time (rate of recovery)		
		10-20s	20-30s	30-110s
Systolic BP				
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]
Diastolic BP				
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]
Heart rate				
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
Systolic BP				
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]
Diastolic BP				
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]
Heart rate				
Slowness	-1.76 [-2.96,-0.55]**	3.26 [2.57,3.96]***	0.47 [-0.26,1.21]	-0.10 [-0.23,0.04]
Activity	0.26 [-0.63,1.16]	0.21 [-0.30,0.73]	0.15 [-0.60,0.90]	0.02 [-0.08,0.12]
Grip	0.29 [-0.84,1.41]	0.53 [-0.12,1.18]	-0.10 [-0.23,0.04]	-0.02 [-0.15,0.11]
Exhaustion	-0.64 [-1.93,0.65]	1.20 [0.46,1.95]**	0.02 [-0.08,0.12]	-0.09 [-0.24,0.06]
Weight loss	0.16 [-1.15,1.47]	0.05 [-0.71,0.80]	-0.02 [-0.15,0.11]	-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.
*P<0.05, **P<0.01, ***P<0.001

Figure legends:

Figure 1: Adjusted blood pressure and heart rate responses across frailty categories

Data are adjusted 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, and are

mutually adjusted for the presence of the other frailty criteria

Figure 2: Conditional differences in percentage blood pressure recovery according to the

presence of each frailty criterion

Differences are relative to the reference not having the criterion. 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
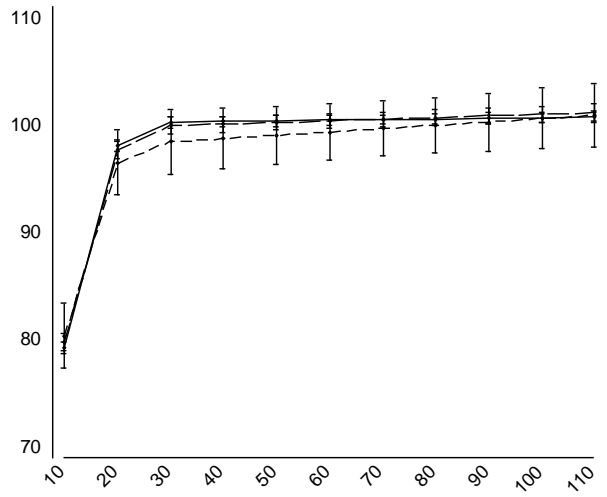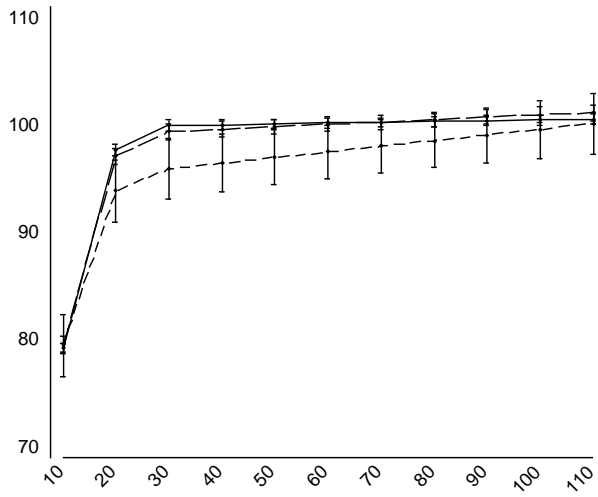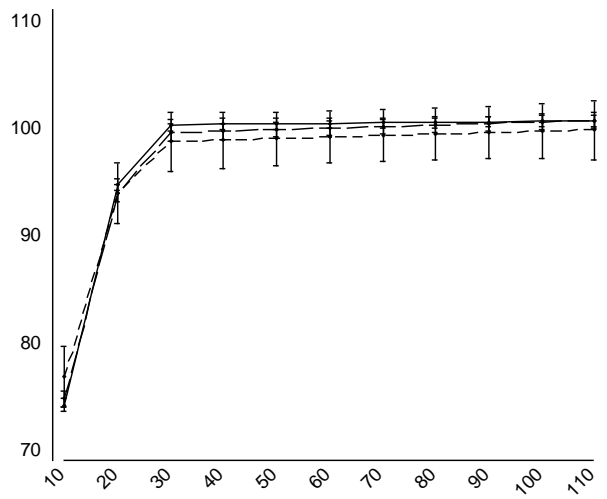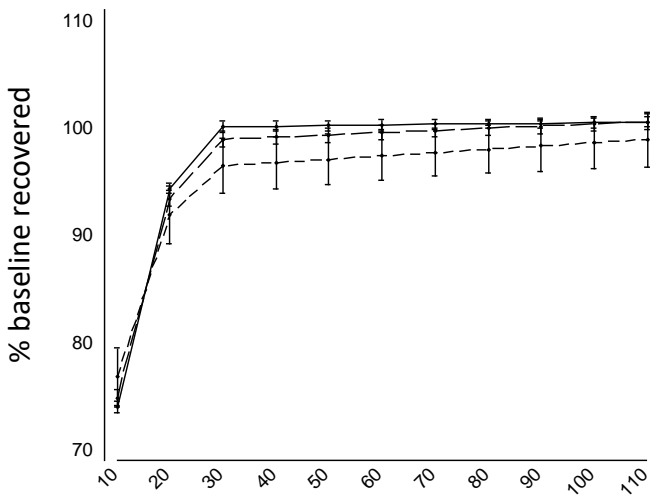
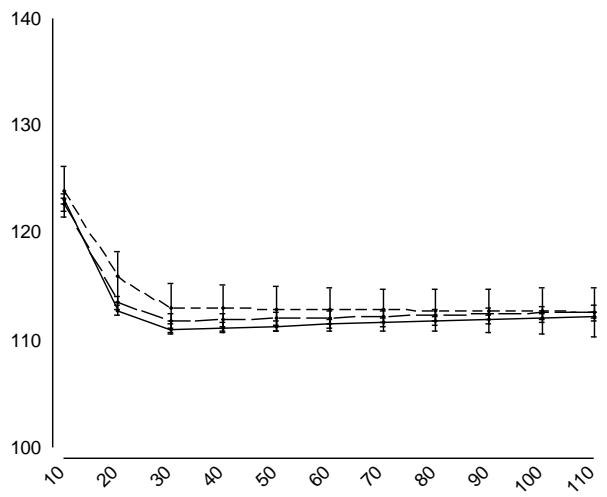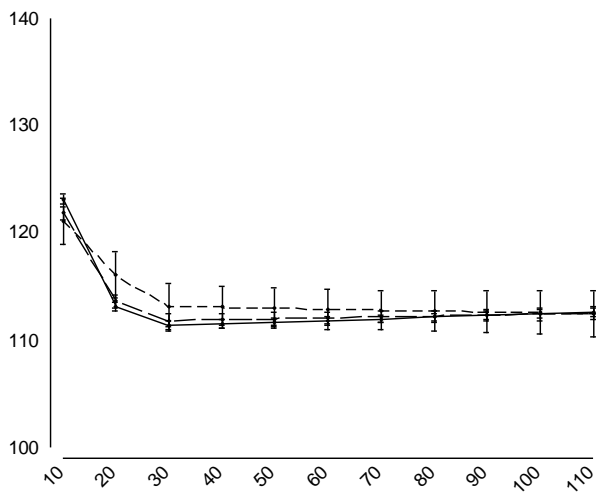frailty criteria.

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Model 1

Model 2

Systolic blood pressure

Diastolic blood pressure

Heart Rate

Time since stand (s)

Conditional difference in % recovered

Time since stand (s)

Supplemental data

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

SBP				
	Model 1		Model 2	
	Prefrail	Frail	Prefrail	Frail
10	0.39 [-0.41,1.20]	0.29 [-2.58,3.17]	0.44 [-0.40,1.28]	1.07 [-1.97,4.10]
20	-0.59 [-1.39,0.21]	-3.83 [-6.69,-0.97]**	-0.44 [-1.28,0.40]	-1.65 [-4.67,1.38]
30	-0.59 [-1.38,0.21]	-4.08 [-6.92,-1.23]**	-0.37 [-1.20,0.46]	-1.93 [-4.94,1.07]
40	-0.44 [-1.19,0.32]	-3.62 [-6.30,-0.94]**	-0.27 [-1.06,0.52]	-1.67 [-4.49,1.16]
50	-0.28 [-1.00,0.44]	-3.16 [-5.71,-0.61]*	-0.17 [-0.92,0.59]	-1.40 [-4.09,1.29]
60	-0.13 [-0.83,0.57]	-2.70 [-5.17,-0.23]*	-0.07 [-0.80,0.67]	-1.13 [-3.73,1.48]
70	0.02 [-0.67,0.71]	-2.24 [-4.69,0.21]	0.04 [-0.69,0.76]	-0.86 [-3.44,1.72]
80	0.17 [-0.53,0.87]	-1.78 [-4.25,0.69]	0.14 [-0.60,0.87]	-0.59 [-3.20,2.02]
90	0.32 [-0.40,1.04]	-1.32 [-3.87,1.23]	0.24 [-0.52,0.99]	-0.32 [-3.01,2.37]
100	0.48 [-0.28,1.23]	-0.86 [-3.54,1.82]	0.34 [-0.45,1.13]	-0.05 [-2.88,2.77]
110	0.63 [-0.17,1.42]	-0.40 [-3.25,2.44]	0.44 [-0.39,1.27]	0.22 [-2.79,3.22]
DBP				
10	0.80 [-0.01,1.61]	2.77 [0.10,5.44]*	0.55 [-0.31,1.40]	2.59 [-0.27,5.45]
20	-1.00 [-1.80,-0.20]*	-2.49 [-5.13,0.15]	-0.84 [-1.69,0.00]	-0.84 [-3.68,1.99]
30	-1.18 [-1.97,-0.39]**	-3.66 [-6.23,-1.09]**	-0.77 [-1.61,0.06]	-1.61 [-4.36,1.15]
40	-1.03 [-1.78,-0.28]**	-3.41 [-5.84,-0.98]**	-0.68 [-1.47,0.11]	-1.52 [-4.11,1.08]
50	-0.88 [-1.60,-0.16]*	-3.16 [-5.47,-0.84]**	-0.58 [-1.34,0.18]	-1.43 [-3.90,1.05]
60	-0.73 [-1.43,-0.03]*	-2.90 [-5.15,-0.65]*	-0.48 [-1.22,0.25]	-1.34 [-3.74,1.06]
70	-0.58 [-1.27,0.11]	-2.65 [-4.88,-0.42]*	-0.38 [-1.11,0.35]	-1.25 [-3.62,1.13]
80	-0.43 [-1.13,0.27]	-2.40 [-4.64,-0.15]*	-0.29 [-1.02,0.45]	-1.16 [-3.56,1.25]
90	-0.28 [-1.00,0.43]	-2.14 [-4.46,0.17]	-0.19 [-0.94,0.57]	-1.06 [-3.54,1.41]
100	-0.13 [-0.88,0.61]	-1.89 [-4.32,0.54]	-0.09 [-0.88,0.70]	-0.97 [-3.57,1.62]
110	0.01 [-0.77,0.80]	-1.64 [-4.21,0.93]	0.01 [-0.82,0.84]	-0.88 [-3.64,1.87]
HR				
10	-1.26 [-1.93,-0.59]***	-2.02 [-4.20,0.16]	-0.51 [-1.22,0.19]	0.70 [-1.64,3.03]
20	0.49 [-0.17,1.15]	2.90 [0.74,5.06]**	0.70 [0.01,1.40]*	3.10 [0.79,5.42]**
30	0.46 [-0.19,1.10]	1.80 [-0.32,3.92]	0.77 [0.10,1.45]*	1.98 [-0.29,4.25]
40	0.39 [-0.22,1.01]	1.56 [-0.45,3.57]	0.74 [0.10,1.39]*	1.80 [-0.35,3.96]
50	0.33 [-0.26,0.92]	1.32 [-0.61,3.25]	0.71 [0.10,1.33]*	1.63 [-0.43,3.69]
60	0.26 [-0.31,0.84]	1.08 [-0.79,2.96]	0.68 [0.08,1.28]*	1.45 [-0.55,3.46]
70	0.20 [-0.37,0.77]	0.85 [-1.02,2.71]	0.65 [0.06,1.25]*	1.28 [-0.70,3.26]
80	0.13 [-0.44,0.71]	0.61 [-1.27,2.48]	0.62 [0.02,1.22]*	1.10 [-0.90,3.11]
90	0.07 [-0.52,0.66]	0.37 [-1.56,2.30]	0.59 [-0.03,1.21]	0.93 [-1.13,2.99]
100	0.00 [-0.61,0.62]	0.13 [-1.88,2.14]	0.56 [-0.08,1.20]	0.76 [-1.40,2.91]
110	-0.06 [-0.71,0.59]	-0.11 [-2.23,2.01]	0.53 [-0.15,1.21]	0.58 [-1.69,2.85]

Parameters are estimated from mixed effects models with linear splines. 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 S2: Model parameters for Blood pressure and heart rate recovery following active standing (Actual values)

	Intercept (10s difference)	Frailty*Time (rate of recovery)		
		10-20s	20-30s	30-110s
Systolic BP (mmHg)				
Model 1				
Prefrail	0.34 [-1.30,1.98]	-1.27 [-1.78,-0.75]***	-0.04 [-0.55,0.47]	0.20 [0.07,0.33]**
Frail	1.27 [-4.66,7.21]	-5.99 [-7.89,-4.09]***	-0.47 [-2.37,1.43]	0.67 [0.13,1.21]*
Model 2				
Prefrail	0.13 [-1.59,1.85]	-1.20 [-1.74,-0.66]***	0.08 [-0.46,0.62]	0.13 [-0.01,0.27]
Frail	0.89 [-5.39,7.17]	-4.47 [-6.49,-2.44]***	-0.46 [-2.49,1.57]	0.43 [-0.14,1.01]
Diastolic BP (mmHg)				
Model 1				
Prefrail	0.10 [-0.74,0.94]	-1.30 [-1.60,-0.99]***	-0.25 [-0.55,0.05]	0.10 [0.04,0.16]**
Frail	1.01 [-1.76,3.78]	-3.87 [-4.99,-2.75]***	-0.93 [-2.03,0.18]	0.20 [-0.03,0.43]
Model 2				
Prefrail	-0.08 [-0.95,0.80]	-1.01 [-1.33,-0.69]***	-0.04 [-0.36,0.28]	0.07 [0.00,0.13]*
Frail	0.32 [-2.59,3.23]	-2.80 [-4.00,-1.60]***	-0.61 [-1.80,0.58]	0.10 [-0.15,0.35]
Heart rate (HR)				
Model 1				
Prefrail	0.92 [0.18,1.67]*	1.03 [0.78,1.29]***	-0.04 [-0.29,0.21]	-0.04 [-0.09,0.01]
Frail	2.09 [-0.32,4.50]	2.99 [2.22,3.76]***	-0.78 [-1.55,-0.01]*	-0.14 [-0.30,0.02]
Model 2				
Prefrail	0.98 [0.22,1.74]*	0.71 [0.44,0.98]***	0.04 [-0.23,0.30]	-0.02 [-0.07,0.03]
Frail	1.42 [-1.05,3.90]	1.45 [0.61,2.29]***	-0.73 [-1.56,0.10]	-0.11 [-0.29,0.07]

Parameters are estimated from mixed effects models with linear splines. Interaction coefficients represent the difference in time 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 S3: Conditional differences in blood pressure or heart rate recovery compared to robust category in mmHg or beats per minute

SBP				
	Model 1		Model 2	
	Prefrail	Frail	Prefrail	Frail
10	0.34 [-1.30,1.98]	1.27 [-4.66,7.21]	0.13 [-1.59,1.85]	0.89 [-5.39,7.17]
20	-0.93 [-2.56,0.71]	-4.72 [-10.65,1.21]	-1.07 [-2.78,0.64]	-3.57 [-9.85,2.70]
30	-0.97 [-2.60,0.66]	-5.19 [-11.11,0.74]	-0.99 [-2.69,0.72]	-4.03 [-10.30,2.24]
40	-0.77 [-2.36,0.83]	-4.52 [-10.27,1.23]	-0.86 [-2.53,0.81]	-3.60 [-9.68,2.48]
50	-0.57 [-2.14,1.00]	-3.85 [-9.47,1.78]	-0.73 [-2.37,0.92]	-3.17 [-9.11,2.78]
60	-0.37 [-1.92,1.18]	-3.18 [-8.72,2.37]	-0.60 [-2.22,1.03]	-2.73 [-8.59,3.12]
70	-0.17 [-1.72,1.37]	-2.51 [-8.02,3.01]	-0.47 [-2.09,1.15]	-2.30 [-8.13,3.53]
80	0.03 [-1.53,1.58]	-1.84 [-7.38,3.71]	-0.34 [-1.96,1.29]	-1.87 [-7.73,3.99]
90	0.23 [-1.34,1.79]	-1.17 [-6.79,4.46]	-0.21 [-1.85,1.43]	-1.44 [-7.38,4.51]
100	0.42 [-1.17,2.02]	-0.50 [-6.25,5.25]	-0.08 [-1.75,1.59]	-1.00 [-7.08,5.08]
110	0.62 [-1.01,2.25]	0.17 [-5.75,6.10]	0.05 [-1.66,1.76]	-0.57 [-6.84,5.70]
DBP				
10	0.10 [-0.74,0.94]	1.01 [-1.76,3.78]	-0.08 [-0.95,0.80]	0.32 [-2.59,3.23]
20	-1.20 [-2.04,-0.37]**	-2.86 [-5.62,-0.10]*	-1.08 [-1.96,-0.21]*	-2.48 [-5.38,0.42]
30	-1.45 [-2.28,-0.62]***	-3.79 [-6.52,-1.06]**	-1.13 [-1.99,-0.27]*	-3.09 [-5.96,-0.22]*
40	-1.35 [-2.16,-0.54]**	-3.59 [-6.25,-0.93]**	-1.06 [-1.91,-0.22]*	-2.99 [-5.78,-0.20]*
50	-1.25 [-2.05,-0.45]**	-3.39 [-6.00,-0.78]*	-0.99 [-1.83,-0.16]*	-2.90 [-5.63,-0.16]*
60	-1.15 [-1.94,-0.36]**	-3.19 [-5.76,-0.61]*	-0.93 [-1.75,-0.10]*	-2.80 [-5.50,-0.10]*
70	-1.05 [-1.83,-0.26]**	-2.99 [-5.55,-0.42]*	-0.86 [-1.68,-0.04]*	-2.70 [-5.39,-0.01]*
80	-0.94 [-1.74,-0.15]*	-2.79 [-5.36,-0.21]*	-0.79 [-1.62,0.03]	-2.60 [-5.30,0.10]
90	-0.84 [-1.64,-0.05]*	-2.59 [-5.20,0.02]	-0.73 [-1.56,0.11]	-2.51 [-5.24,0.23]
100	-0.74 [-1.55,0.07]	-2.39 [-5.05,0.27]	-0.66 [-1.50,0.19]	-2.41 [-5.20,0.38]
110	-0.64 [-1.47,0.19]	-2.19 [-4.92,0.54]	-0.59 [-1.45,0.27]	-2.31 [-5.18,0.56]
HR				
10	0.92 [0.18,1.67]*	2.09 [-0.32,4.50]	0.98 [0.22,1.74]*	1.42 [-1.05,3.90]
20	1.96 [1.21,2.70]***	5.08 [2.68,7.48]***	1.69 [0.94,2.45]***	2.87 [0.40,5.34]*
30	1.92 [1.18,2.65]***	4.30 [1.91,6.69]***	1.73 [0.98,2.48]***	2.15 [-0.30,4.60]
40	1.88 [1.16,2.60]***	4.16 [1.81,6.51]***	1.71 [0.98,2.45]***	2.04 [-0.37,4.44]
50	1.84 [1.13,2.56]***	4.02 [1.70,6.34]***	1.70 [0.97,2.42]***	1.93 [-0.45,4.30]
60	1.81 [1.10,2.52]***	3.88 [1.58,6.18]***	1.68 [0.96,2.40]***	1.82 [-0.54,4.17]
70	1.77 [1.06,2.48]***	3.74 [1.44,6.03]**	1.66 [0.94,2.38]***	1.71 [-0.64,4.06]
80	1.73 [1.02,2.44]***	3.59 [1.29,5.89]**	1.65 [0.93,2.37]***	1.60 [-0.75,3.95]
90	1.70 [0.98,2.41]***	3.45 [1.13,5.77]**	1.63 [0.91,2.36]***	1.49 [-0.88,3.86]
100	1.66 [0.94,2.39]***	3.31 [0.96,5.66]**	1.62 [0.88,2.35]***	1.38 [-1.02,3.79]
110	1.63 [0.89,2.36]***	3.17 [0.78,5.56]**	1.60 [0.85,2.35]***	1.27 [-1.18,3.72]

Parameters are estimated from mixed effects models with linear splines. 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

Figure S1: Adjusted blood pressure and heart rate responses across frailty categories

Data are adjusted 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, and are mutually adjusted for the presence of the other frailty criteria
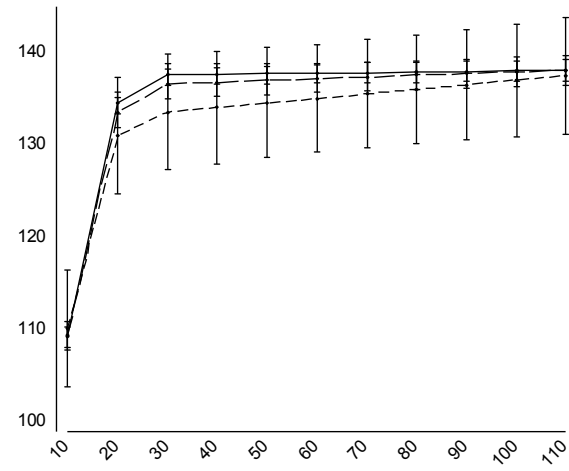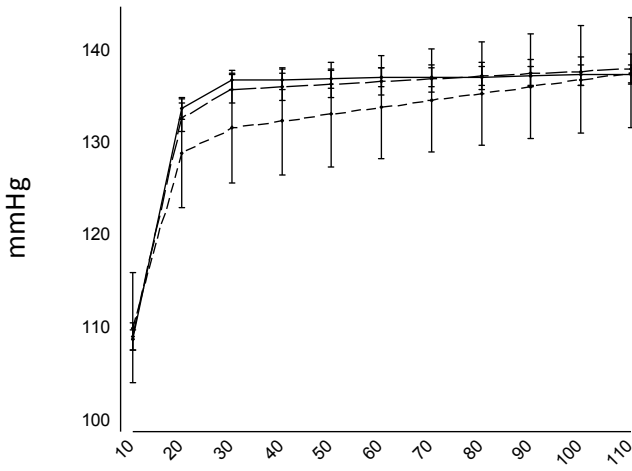
———— Robust   − − − − − Prefrail   - - - - - - - Frail

Model 1

Model 2

Systolic blood pressure

Diastolic blood pressure
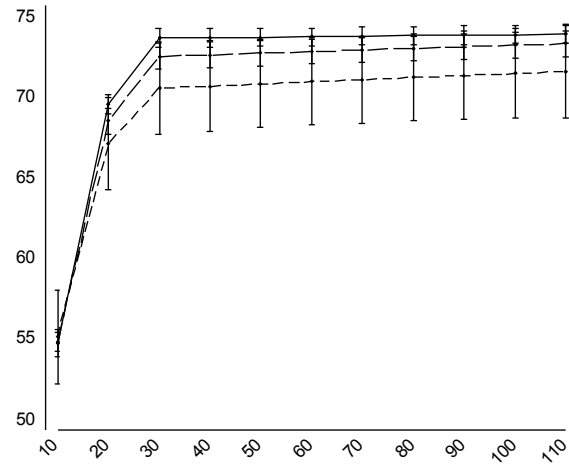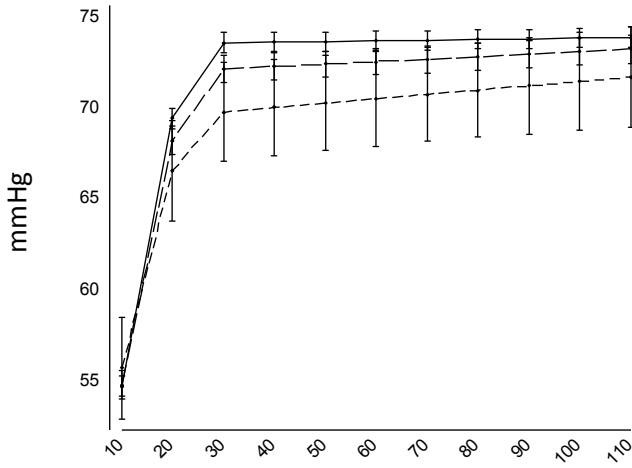
Heart Rate
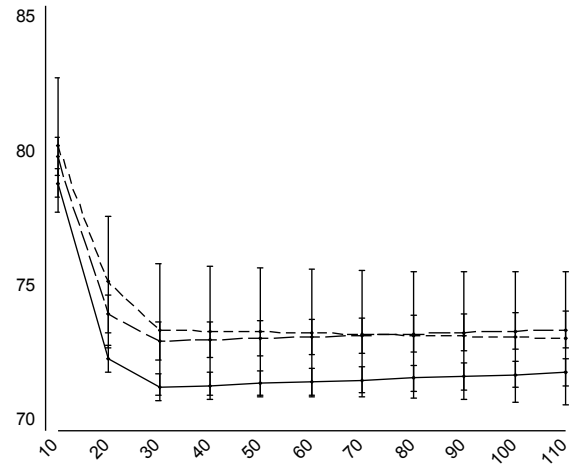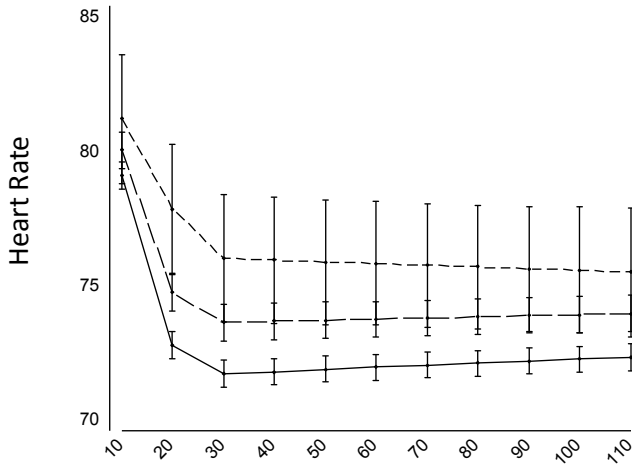
Time since stand (s)

Appendix Tables – Full model outputs

Table SA1: Mixed effects models for % SBP recovery

Main effects	Model 1	Model 2
Period 1 10-20s	1.71 (-7.43 - 10.84)	-16.56 (-26.41 - -6.71)
Period 2 20-30s	-4.07 (-13.18 - 5.04)	2.02 (-7.81 - 11.85)
Period 3 30-110s	-1.61 (-3.81 - 0.59)	-0.43 (-2.80 - 1.95)
Prefrail	0.39 (-0.41 - 1.20)	0.44 (-0.40 - 1.28)
Frail	0.29 (-2.58 - 3.17)	1.07 (-1.97 - 4.10)
Age	-0.42 (-1.01 - 0.17)	-0.52 (-1.11 - 0.07)
Age*age	0.00 (0.00 - 0.01)	0.00 (0.00 - 0.01)
Female	-1.56 (-2.27 - -0.85)	-1.14 (-1.88 - -0.40)
Antidepressant		-3.84 (-5.44 - -2.25)
Antihypertensive		-3.05 (-4.24 - -1.86)
BMI		0.77 (0.29 - 1.24)
BMI*BMI		-0.01 (-0.02 - 0.00)
Past smoker		0.50 (-0.28 - 1.27)
Current smoker		-0.10 (-1.18 - 0.98)
CES-D score		-0.01 (-0.07 - 0.06)
Diabetes		1.51 (-0.01 - 3.03)
Stroke		-2.25 (-5.86 - 1.35)
Angina		-2.77 (-4.71 - -0.83)
Heart attack		1.42 (-0.60 - 3.43)
Hypertension		1.17 (0.35 - 2.00)
Heart murmur		-0.31 (-1.94 - 1.32)
Interactions 10-20s		
Prefrail*time	-0.99 (-1.37 - -0.60)	-0.88 (-1.29 - -0.47)
Frail*time	-4.12 (-5.53 - -2.72)	-2.71 (-4.21 - -1.21)
Age*time	0.81 (0.52 - 1.10)	0.89 (0.59 - 1.18)
Age*age*time	-0.01 (-0.01 - -0.01)	-0.01 (-0.01 - -0.01)
Female*time	-2.01 (-2.36 - -1.67)	-1.60 (-1.96 - -1.23)
Antidepressant*time		-0.62 (-1.40 - 0.16)
Antihypertensive*time		0.02 (-0.57 - 0.61)
BMI*time		0.98 (0.75 - 1.22)
BMI*BMI*time		-0.01 (-0.02 - -0.01)
Past smoker*time		-0.51 (-0.89 - -0.13)
Current smoker*time		-2.03 (-2.56 - -1.50)
CES-D score*time		-0.03 (-0.06 - 0.00)
Diabetes*time		-0.62 (-1.37 - 0.13)
Stroke*time		1.01 (-0.75 - 2.76)
Angina*time		1.42 (0.47 - 2.37)
Heart attack*time		1.05 (0.06 - 2.04)
Hypertension*time		-2.12 (-2.53 - -1.72)
Heart murmur*time		0.92 (0.11 - 1.72)
Interactions 20-30s		
Prefrail*time	0.01 (-0.38 - 0.39)	0.07 (-0.34 - 0.48)
Frail*time	-0.25 (-1.65 - 1.15)	-0.29 (-1.79 - 1.21)
Age*time	0.05 (-0.24 - 0.33)	0.00 (-0.30 - 0.29)
Age*age*time	0.00 (0.00 - 0.00)	0.00 (0.00 - 0.00)
Female*time	1.68 (1.34 - 2.03)	1.56 (1.20 - 1.92)
Antidepressant*time		0.92 (0.14 - 1.69)
Antihypertensive*time		0.86 (0.27 - 1.44)

BMI*time		-0.19 (-0.42 - 0.05)
BMI*BMI*time		0.00 (0.00 - 0.00)
Past smoker*time		-0.21 (-0.59 - 0.17)
Current smoker*time		0.45 (-0.08 - 0.98)
CES-D score*time		-0.02 (-0.05 - 0.01)
Diabetes*time		-1.10 (-1.85 - -0.36)
Stroke*time		0.73 (-1.03 - 2.48)
Angina*time		0.74 (-0.20 - 1.69)
Heart attack*time		-0.50 (-1.49 - 0.49)
Hypertension*time		0.74 (0.33 - 1.15)
Heart murmur*time		0.20 (-0.60 - 1.00)
Interactions 30-110s		
Prefrail*time	0.15 (0.06 - 0.25)	0.10 (0.00 - 0.20)
Frail*time	0.46 (0.10 - 0.82)	0.27 (-0.12 - 0.66)
Age*time	0.02 (-0.05 - 0.09)	0.02 (-0.05 - 0.09)
Age*age*time	0.00 (0.00 - 0.00)	0.00 (0.00 - 0.00)
Female*time	0.06 (-0.02 - 0.14)	0.04 (-0.05 - 0.12)
Antidepressant*time		0.16 (-0.03 - 0.35)
Antihypertensive*time		0.01 (-0.13 - 0.16)
BMI*time		-0.08 (-0.13 - -0.02)
BMI*BMI*time		0.00 (0.00 - 0.00)
Past smoker*time		0.03 (-0.06 - 0.13)
Current smoker*time		0.19 (0.06 - 0.32)
CES-D score*time		0.01 (0.00 - 0.01)
Diabetes*time		0.13 (-0.05 - 0.31)
Stroke*time		-0.11 (-0.55 - 0.33)
Angina*time		0.13 (-0.10 - 0.36)
Heart attack*time		-0.01 (-0.25 - 0.23)
Hypertension*time		0.07 (-0.03 - 0.17)
Heart murmur*time		0.12 (-0.07 - 0.31)
Intercept	95.91 (77.18 - 114.63)	83.24 (63.23 - 103.25)
Random effects (identity matrix)		
Intercept variance	71.96 (67.17 - 77.09)	67.87 (63.18 - 72.92)
AR1 Residuals by Frailty category		
variance		
Robust	61.68 (58.53 - 64.98)	61.49 (58.31 - 64.84)
Prefrail	89.55 (82.26 - 97.49)	90.61 (83.17 - 98.72)
Frail	120.38 (90.48 - 160.17)	124.69 (92.53 - 168.02)
rho		
Robust	0.74 (0.72 - 0.75)	0.74 (0.73 - 0.75)
Prefrail	0.80 (0.78 - 0.81)	0.80 (0.78 - 0.82)
Frail	0.81 (0.75 - 0.86)	0.81 (0.75 - 0.86)

Table SA2: Mixed effects models for % DBP recovery

Main effects	Model 1	Model 2
Period 1 10-20s	12.04 (1.71 - 22.37)	3.03 (-8.12 - 14.17)
Period 2 20-30s	-3.84 (-14.10 - 6.41)	3.82 (-7.24 - 14.89)
Period 3 30-110s	-1.16 (-3.32 - 0.99)	-0.35 (-2.68 - 1.97)
Prefrail	0.80 (-0.01 - 1.61)	0.55 (-0.31 - 1.40)
Frail	2.77 (0.10 - 5.44)	2.59 (-0.27 - 5.45)
Age	-0.62 (-1.21 - -0.02)	-0.72 (-1.32 - -0.12)
Age*age	0.00 (0.00 - 0.01)	0.00 (0.00 - 0.01)
Female	0.34 (-0.38 - 1.06)	0.68 (-0.07 - 1.44)
Antidepressant		-2.35 (-3.97 - -0.73)
Antihypertensive		-2.87 (-4.08 - -1.65)
BMI		0.90 (0.42 - 1.39)
BMI*BMI		-0.01 (-0.02 - 0.00)
Past smoker		0.46 (-0.33 - 1.26)
Current smoker		0.76 (-0.35 - 1.87)
CES-D score		0.03 (-0.03 - 0.10)
Diabetes		1.26 (-0.29 - 2.81)
Stroke		-3.08 (-6.71 - 0.54)
Angina		-3.67 (-5.64 - -1.70)
Heart attack		0.54 (-1.52 - 2.59)
Hypertension		1.32 (0.47 - 2.17)
Heart murmur		-1.25 (-2.92 - 0.42)
Interactions 10-20s		
Prefrail*time	-1.80 (-2.24 - -1.36)	-1.39 (-1.86 - -0.92)
Frail*time	-5.26 (-6.87 - -3.65)	-3.44 (-5.16 - -1.71)
Age*time	0.63 (0.30 - 0.96)	0.80 (0.48 - 1.13)
Age*age*time	-0.01 (-0.01 - -0.01)	-0.01 (-0.01 - -0.01)
Female*time	-3.18 (-3.58 - -2.79)	-3.08 (-3.50 - -2.67)
Antidepressant*time		-0.18 (-1.06 - 0.71)
Antihypertensive*time		0.15 (-0.51 - 0.81)
BMI*time		0.41 (0.15 - 0.68)
BMI*BMI*time		-0.01 (-0.01 - 0.00)
Past smoker*time		-0.96 (-1.39 - -0.53)
Current smoker*time		-2.02 (-2.63 - -1.42)
CES-D score*time		-0.06 (-0.09 - -0.02)
Diabetes*time		-1.57 (-2.42 - -0.72)
Stroke*time		3.00 (1.00 - 5.01)
Angina*time		1.68 (0.61 - 2.76)
Heart attack*time		2.33 (1.21 - 3.45)
Hypertension*time		-2.30 (-2.76 - -1.84)
Heart murmur*time		-0.51 (-1.42 - 0.39)
Interactions 20-30s		
Prefrail*time	-0.18 (-0.62 - 0.26)	0.07 (-0.40 - 0.53)
Frail*time	-1.17 (-2.77 - 0.42)	-0.76 (-2.47 - 0.95)
Age*time	0.13 (-0.19 - 0.45)	0.10 (-0.22 - 0.43)
Age*age*time	0.00 (0.00 - 0.00)	0.00 (0.00 - 0.00)
Female*time	2.81 (2.43 - 3.20)	2.65 (2.24 - 3.06)
Antidepressant*time		0.09 (-0.79 - 0.97)
Antihypertensive*time		0.83 (0.17 - 1.49)
BMI*time		-0.27 (-0.53 - -0.01)

For Review Only

BMI*BMI*time		0.00 (0.00 - 0.01)
Past smoker*time		-0.33 (-0.76 - 0.10)
Current smoker*time		-0.53 (-1.12 - 0.07)
CES-D score*time		-0.02 (-0.06 - 0.02)
Diabetes*time		-1.31 (-2.15 - -0.47)
Stroke*time		0.00 (-1.99 - 1.99)
Angina*time		1.19 (0.12 - 2.26)
Heart attack*time		-0.62 (-1.73 - 0.50)
Hypertension*time		0.73 (0.27 - 1.18)
Heart murmur*time		0.36 (-0.54 - 1.26)
Interactions 30-110s		
Prefrail*time	0.15 (0.05 - 0.24)	0.10 (0.00 - 0.20)
Frail*time	0.25 (-0.07 - 0.58)	0.09 (-0.26 - 0.44)
Age*time	0.01 (-0.05 - 0.08)	0.01 (-0.06 - 0.08)
Age*age*time	0.00 (0.00 - 0.00)	0.00 (0.00 - 0.00)
Female*time	0.08 (0.00 - 0.16)	0.06 (-0.03 - 0.15)
Antidepressant*time		0.11 (-0.08 - 0.30)
Antihypertensive*time		0.05 (-0.09 - 0.19)
BMI*time		-0.05 (-0.11 - 0.00)
BMI*BMI*time		0.00 (0.00 - 0.00)
Past smoker*time		0.05 (-0.04 - 0.14)
Current smoker*time		0.12 (0.00 - 0.25)
CES-D score*time		0.01 (0.00 - 0.02)
Diabetes*time		0.12 (-0.06 - 0.30)
Stroke*time		-0.20 (-0.62 - 0.23)
Angina*time		0.06 (-0.17 - 0.29)
Heart attack*time		-0.08 (-0.32 - 0.15)
Hypertension*time		0.04 (-0.06 - 0.13)
Heart murmur*time		0.20 (0.01 - 0.39)
Intercept	96.75 (77.80 - 115.71)	80.22 (59.81 - 100.62)
Random effects (identity matrix)		
Intercept variance	83.37 (78.87 - 88.13)	82.05 (77.58 - 86.79)
AR1 Residuals by Frailty category		
variance		
Robust	58.03 (55.80 - 60.36)	57.52 (55.29 - 59.83)
Prefrail	78.61 (73.63 - 83.92)	77.20 (72.26 - 82.48)
Frail	81.71 (66.37 - 100.59)	85.43 (68.54 - 106.48)
rho		
Robust	0.65 (0.64 - 0.66)	0.65 (0.64 - 0.66)
Prefrail	0.69 (0.67 - 0.71)	0.69 (0.67 - 0.71)
Frail	0.63 (0.54 - 0.70)	0.63 (0.54 - 0.71)

Table SA3: Mixed effects models for % HR recovery

Main effects	Model 1	Model 2
Period 1 10-20s	-69.39 (-78.50 - -60.28)	-44.75 (-54.57 - -34.92)
Period 2 20-30s	28.21 (19.19 - 37.23)	28.81 (19.09 - 38.53)
Period 3 30-110s	1.67 (-0.16 - 3.50)	2.25 (0.30 - 4.21)
Prefrail	-1.26 (-1.93 - -0.59)	-0.51 (-1.22 - 0.19)
Frail	-2.02 (-4.20 - 0.16)	0.70 (-1.64 - 3.03)
Age	-0.68 (-1.18 - -0.17)	-0.52 (-1.03 - -0.02)
Age*age	0.00 (0.00 - 0.01)	0.00 (0.00 - 0.01)
Female	-1.17 (-1.78 - -0.56)	-1.25 (-1.89 - -0.61)
Antidepressant		-3.53 (-4.88 - -2.18)
Antihypertensive		-2.52 (-3.54 - -1.50)
BMI		0.77 (0.36 - 1.18)
BMI*BMI		-0.01 (-0.02 - 0.00)
Past smoker		0.00 (-0.67 - 0.67)
Current smoker		-2.80 (-3.73 - -1.87)
CES-D score		0.00 (-0.05 - 0.06)
Diabetes		-3.31 (-4.60 - -2.02)
Stroke		-0.31 (-3.29 - 2.67)
Angina		-1.35 (-2.99 - 0.29)
Heart attack		-0.98 (-2.69 - 0.73)
Hypertension		-2.14 (-2.85 - -1.42)
Heart murmur		0.48 (-0.92 - 1.89)
Interactions 10-20s		
Prefrail*time	1.74 (1.36 - 2.13)	1.22 (0.81 - 1.62)
Frail*time	4.92 (3.73 - 6.11)	2.41 (1.12 - 3.70)
Age*time	1.45 (1.16 - 1.73)	1.38 (1.09 - 1.67)
Age*age*time	-0.01 (-0.01 - -0.01)	-0.01 (-0.01 - 0.00)
Female*time	-0.64 (-0.98 - -0.29)	-0.91 (-1.27 - -0.54)
Antidepressant*time		2.49 (1.72 - 3.27)
Antihypertensive*time		-0.17 (-0.76 - 0.42)
BMI*time		-1.53 (-1.76 - -1.29)
BMI*BMI*time		0.02 (0.02 - 0.03)
Past smoker*time		0.48 (0.09 - 0.86)
Current smoker*time		3.86 (3.32 - 4.39)
CES-D score*time		0.02 (-0.01 - 0.05)
Diabetes*time		1.67 (0.92 - 2.41)
Stroke*time		0.43 (-1.29 - 2.15)
Angina*time		1.32 (0.37 - 2.26)
Heart attack*time		0.94 (-0.05 - 1.93)
Hypertension*time		1.79 (1.38 - 2.20)
Heart murmur*time		-0.50 (-1.31 - 0.31)
Interactions 20-30s		
Prefrail*time	-0.03 (-0.41 - 0.35)	0.07 (-0.33 - 0.47)
Frail*time	-1.10 (-2.29 - 0.08)	-1.12 (-2.40 - 0.16)
Age*time	-0.90 (-1.19 - -0.62)	-0.89 (-1.18 - -0.61)
Age*age*time	0.01 (0.00 - 0.01)	0.01 (0.00 - 0.01)
Female*time	0.27 (-0.08 - 0.61)	0.24 (-0.13 - 0.60)
Antidepressant*time		0.39 (-0.38 - 1.15)
Antihypertensive*time		0.32 (-0.26 - 0.90)
BMI*time		0.00 (-0.23 - 0.24)

BMI*BMI*time		0.00 (0.00 - 0.00)
Past smoker*time		-0.03 (-0.41 - 0.35)
Current smoker*time		0.18 (-0.35 - 0.71)
CES-D score*time		-0.02 (-0.05 - 0.01)
Diabetes*time		0.72 (-0.02 - 1.46)
Stroke*time		0.17 (-1.53 - 1.88)
Angina*time		-1.07 (-2.01 - -0.13)
Heart attack*time		-0.02 (-1.00 - 0.95)
Hypertension*time		-0.16 (-0.57 - 0.25)
Heart murmur*time		-0.82 (-1.62 - -0.02)
Interactions 30-110s		
Prefrail*time	-0.06 (-0.14 - 0.01)	-0.03 (-0.11 - 0.05)
Frail*time	-0.24 (-0.49 - 0.01)	-0.17 (-0.45 - 0.10)
Age*time	-0.02 (-0.08 - 0.03)	-0.01 (-0.07 - 0.05)
Age*age*time	0.00 (0.00 - 0.00)	0.00 (0.00 - 0.00)
Female*time	0.06 (-0.01 - 0.13)	0.02 (-0.05 - 0.10)
Antidepressant*time		0.01 (-0.14 - 0.17)
Antihypertensive*time		-0.10 (-0.21 - 0.02)
BMI*time		-0.04 (-0.09 - 0.00)
BMI*BMI*time		0.00 (0.00 - 0.00)
Past smoker*time		-0.04 (-0.11 - 0.04)
Current smoker*time		-0.11 (-0.22 - -0.01)
CES-D score*time		0.00 (-0.01 - 0.01)
Diabetes*time		-0.08 (-0.22 - 0.07)
Stroke*time		0.12 (-0.22 - 0.46)
Angina*time		-0.04 (-0.23 - 0.15)
Heart attack*time		0.09 (-0.11 - 0.28)
Hypertension*time		-0.05 (-0.13 - 0.03)
Heart murmur*time		-0.03 (-0.19 - 0.13)
Intercept	157.26 (141.30 - 173.22)	140.17 (123.09 - 157.26)
Random effects (identity matrix)		
Intercept variance	58.73 (55.59 - 62.06)	57.37 (54.29 - 60.62)
AR1 Residuals by Frailty category		
variance		
Robust	46.94 (45.15 - 48.80)	45.25 (43.56 - 47.01)
Prefrail	47.74 (45.23 - 50.38)	46.34 (43.93 - 48.89)
Frail	50.39 (40.40 - 62.85)	53.21 (41.96 - 67.48)
rho		
Robust	0.64 (0.62 - 0.65)	0.63 (0.61 - 0.64)
Prefrail	0.63 (0.61 - 0.65)	0.62 (0.60 - 0.64)
Frail	0.68 (0.60 - 0.75)	0.69 (0.60 - 0.76)

Table SA4: Mixed effects models for SBP recovery

Main effects	Model 1	Model 2
Period 1 10-20s	-15.43 (-27.53 - -3.32)	-40.89 (-53.94 - -27.84)
Period 2 20-30s	-6.85 (-18.93 - 5.23)	-0.21 (-13.24 - 12.81)
Period 3 30-110s	-1.10 (-4.03 - 1.83)	0.26 (-2.91 - 3.43)
Prefrail	0.34 (-1.30 - 1.98)	0.13 (-1.59 - 1.85)
Frail	1.27 (-4.66 - 7.21)	0.89 (-5.39 - 7.17)
Age	1.37 (0.15 - 2.60)	0.97 (-0.25 - 2.19)
Age*age	-0.01 (-0.02 - 0.00)	-0.01 (-0.01 - 0.00)
Female	0.63 (-0.84 - 2.10)	0.56 (-0.97 - 2.09)
Antidepressant		-3.46 (-6.74 - -0.18)
Antihypertensive		-5.89 (-8.35 - -3.42)
BMI		1.68 (0.70 - 2.67)
BMI*BMI		-0.02 (-0.04 - -0.01)
Past smoker		-0.80 (-2.41 - 0.80)
Current smoker		-2.80 (-5.05 - -0.56)
CES-D score		0.12 (-0.01 - 0.26)
Diabetes		0.66 (-2.48 - 3.79)
Stroke		-3.23 (-10.58 - 4.12)
Angina		-6.88 (-10.87 - -2.90)
Heart attack		-2.29 (-6.45 - 1.86)
Hypertension		5.43 (3.71 - 7.15)
Heart murmur		-2.75 (-6.13 - 0.63)
Interactions 10-20s		
Prefrail*time	-1.27 (-1.78 - -0.75)	-1.20 (-1.74 - -0.66)
Frail*time	-5.99 (-7.89 - -4.09)	-4.47 (-6.49 - -2.44)
Age*time	1.57 (1.19 - 1.95)	1.59 (1.21 - 1.98)
Age*age*time	-0.01 (-0.02 - -0.01)	-0.01 (-0.02 - -0.01)
Female*time	-2.26 (-2.72 - -1.80)	-1.77 (-2.25 - -1.29)
Antidepressant*time		-0.30 (-1.33 - 0.74)
Antihypertensive*time		-0.20 (-0.98 - 0.57)
BMI*time		1.50 (1.19 - 1.81)
BMI*BMI*time		-0.02 (-0.03 - -0.02)
Past smoker*time		-0.85 (-1.36 - -0.35)
Current smoker*time		-3.21 (-3.91 - -2.50)
CES-D score*time		-0.02 (-0.06 - 0.02)
Diabetes*time		-1.09 (-2.08 - -0.10)
Stroke*time		0.29 (-2.04 - 2.61)
Angina*time		1.29 (0.04 - 2.55)
Heart attack*time		0.52 (-0.79 - 1.83)
Hypertension*time		-1.92 (-2.46 - -1.38)
Heart murmur*time		1.18 (0.12 - 2.25)
Interactions 20-30s		
Prefrail*time	-0.04 (-0.55 - 0.47)	0.08 (-0.46 - 0.62)
Frail*time	-0.47 (-2.37 - 1.43)	-0.46 (-2.49 - 1.57)
Age*time	0.10 (-0.28 - 0.48)	0.03 (-0.36 - 0.41)
Age*age*time	0.00 (0.00 - 0.00)	0.00 (0.00 - 0.00)
Female*time	2.35 (1.89 - 2.81)	2.19 (1.70 - 2.67)
Antidepressant*time		1.33 (0.30 - 2.36)
Antihypertensive*time		1.11 (0.34 - 1.89)
BMI*time		-0.14 (-0.45 - 0.17)

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BMI*BMI*time		0.00 (-0.01 - 0.00)
Past smoker*time		-0.26 (-0.76 - 0.24)
Current smoker*time		0.44 (-0.27 - 1.14)
CES-D score*time		-0.02 (-0.07 - 0.02)
Diabetes*time		-1.58 (-2.56 - -0.59)
Stroke*time		0.90 (-1.42 - 3.22)
Angina*time		0.79 (-0.47 - 2.04)
Heart attack*time		-1.15 (-2.46 - 0.15)
Hypertension*time		1.11 (0.57 - 1.65)
Heart murmur*time		0.19 (-0.87 - 1.25)
Interactions 30-110s		
Prefrail*time	0.20 (0.07 - 0.33)	0.13 (-0.01 - 0.27)
Frail*time	0.67 (0.13 - 1.21)	0.43 (-0.14 - 1.01)
Age*time	-0.01 (-0.10 - 0.09)	-0.01 (-0.10 - 0.08)
Age*age*time	0.00 (0.00 - 0.00)	0.00 (0.00 - 0.00)
Female*time	0.09 (-0.02 - 0.20)	0.06 (-0.06 - 0.17)
Antidepressant*time		0.20 (-0.06 - 0.45)
Antihypertensive*time		0.03 (-0.15 - 0.22)
BMI*time		-0.09 (-0.17 - -0.02)
BMI*BMI*time		0.00 (0.00 - 0.00)
Past smoker*time		0.04 (-0.08 - 0.16)
Current smoker*time		0.27 (0.10 - 0.44)
CES-D score*time		0.01 (0.00 - 0.02)
Diabetes*time		0.15 (-0.10 - 0.39)
Stroke*time		-0.05 (-0.64 - 0.53)
Angina*time		0.14 (-0.16 - 0.45)
Heart attack*time		-0.03 (-0.35 - 0.29)
Hypertension*time		0.07 (-0.06 - 0.20)
Heart murmur*time		0.15 (-0.11 - 0.41)
Intercept	56.08 (17.29 - 94.88)	37.26 (-4.15 - 78.67)
Random effects (identity matrix)		
Intercept variance	484.80 (461.61 - 509.15)	464.58 (441.81 - 488.53)
AR1 Residuals by Frailty category		
variance		
Robust	107.04 (101.53 - 112.84)	106.44 (100.90 - 112.30)
Prefrail	162.61 (146.42 - 180.58)	167.18 (149.73 - 186.68)
Frail	329.37 (180.59 - 600.72)	352.45 (181.23 - 685.46)
rho		
Robust	0.74 (0.72 - 0.75)	0.74 (0.72 - 0.75)
Prefrail	0.80 (0.78 - 0.82)	0.81 (0.79 - 0.83)
Frail	0.87 (0.77 - 0.93)	0.88 (0.77 - 0.94)

Table SA5: Mixed effects models for DBP recovery

Main effects	Model 1	Model 2
Period 1 10-20s	8.44 (1.24 - 15.63)	2.40 (-5.36 - 10.16)
Period 2 20-30s	-3.33 (-10.46 - 3.80)	1.81 (-5.88 - 9.51)
Period 3 30-110s	-0.74 (-2.21 - 0.73)	-0.30 (-1.88 - 1.28)
Prefrail	0.10 (-0.74 - 0.94)	-0.08 (-0.95 - 0.80)
Frail	1.01 (-1.76 - 3.78)	0.32 (-2.59 - 3.23)
Age	-0.17 (-0.80 - 0.46)	-0.35 (-0.98 - 0.27)
Age*age	0.00 (0.00 - 0.01)	0.00 (0.00 - 0.01)
Female	-1.25 (-2.01 - -0.49)	-1.41 (-2.20 - -0.62)
Antidepressant		-0.61 (-2.28 - 1.06)
Antihypertensive		-4.19 (-5.45 - -2.92)
BMI		0.84 (0.34 - 1.34)
BMI*BMI		-0.01 (-0.02 - 0.00)
Past smoker		-0.22 (-1.04 - 0.61)
Current smoker		-0.62 (-1.77 - 0.53)
CES-D score		0.07 (0.00 - 0.14)
Diabetes		-0.79 (-2.39 - 0.81)
Stroke		-1.90 (-5.61 - 1.81)
Angina		-4.03 (-6.07 - -1.99)
Heart attack		-2.59 (-4.71 - -0.46)
Hypertension		2.39 (1.51 - 3.28)
Heart murmur		-2.26 (-4.00 - -0.53)
Interactions 10-20s		
Prefrail*time	-1.30 (-1.60 - -0.99)	-1.01 (-1.33 - -0.69)
Frail*time	-3.87 (-4.99 - -2.75)	-2.80 (-4.00 - -1.60)
Age*time	0.48 (0.25 - 0.71)	0.57 (0.34 - 0.80)
Age*age*time	-0.01 (-0.01 - 0.00)	-0.01 (-0.01 - 0.00)
Female*time	-2.84 (-3.11 - -2.57)	-2.87 (-3.15 - -2.58)
Antidepressant*time		0.30 (-0.32 - 0.91)
Antihypertensive*time		-0.47 (-0.93 - -0.01)
BMI*time		0.31 (0.12 - 0.49)
BMI*BMI*time		-0.01 (-0.01 - 0.00)
Past smoker*time		-0.76 (-1.06 - -0.46)
Current smoker*time		-1.69 (-2.11 - -1.27)
CES-D score*time		-0.03 (-0.06 - -0.01)
Diabetes*time		-1.33 (-1.92 - -0.74)
Stroke*time		1.69 (0.30 - 3.08)
Angina*time		0.71 (-0.04 - 1.46)
Heart attack*time		0.67 (-0.11 - 1.45)
Hypertension*time		-1.26 (-1.58 - -0.94)
Heart murmur*time		-0.47 (-1.10 - 0.16)
Interactions 20-30s		
Prefrail*time	-0.25 (-0.55 - 0.05)	-0.04 (-0.36 - 0.28)
Frail*time	-0.93 (-2.03 - 0.18)	-0.61 (-1.80 - 0.58)
Age*time	0.12 (-0.11 - 0.35)	0.09 (-0.13 - 0.32)
Age*age*time	0.00 (0.00 - 0.00)	0.00 (0.00 - 0.00)
Female*time	1.94 (1.67 - 2.21)	1.80 (1.51 - 2.08)
Antidepressant*time		0.16 (-0.45 - 0.77)
Antihypertensive*time		0.51 (0.06 - 0.97)
BMI*time		-0.15 (-0.34 - 0.03)

BMI*BMI*time		0.00 (0.00 - 0.00)
Past smoker*time		-0.23 (-0.52 - 0.07)
Current smoker*time		-0.51 (-0.92 - -0.09)
CES-D score*time		-0.01 (-0.04 - 0.01)
Diabetes*time		-1.08 (-1.67 - -0.50)
Stroke*time		-0.12 (-1.49 - 1.25)
Angina*time		0.59 (-0.15 - 1.33)
Heart attack*time		-0.63 (-1.41 - 0.14)
Hypertension*time		0.64 (0.32 - 0.96)
Heart murmur*time		0.14 (-0.48 - 0.77)
Interactions 30-110s		
Prefrail*time	0.10 (0.04 - 0.16)	0.07 (0.00 - 0.13)
Frail*time	0.20 (-0.03 - 0.43)	0.10 (-0.15 - 0.35)
Age*time	0.01 (-0.04 - 0.05)	0.01 (-0.04 - 0.05)
Age*age*time	0.00 (0.00 - 0.00)	0.00 (0.00 - 0.00)
Female*time	0.06 (0.00 - 0.11)	0.04 (-0.01 - 0.10)
Antidepressant*time		0.08 (-0.05 - 0.21)
Antihypertensive*time		0.04 (-0.05 - 0.14)
BMI*time		-0.03 (-0.07 - 0.01)
BMI*BMI*time		0.00 (0.00 - 0.00)
Past smoker*time		0.04 (-0.02 - 0.10)
Current smoker*time		0.09 (0.01 - 0.18)
CES-D score*time		0.00 (0.00 - 0.01)
Diabetes*time		0.06 (-0.06 - 0.18)
Stroke*time		-0.07 (-0.36 - 0.21)
Angina*time		0.02 (-0.14 - 0.17)
Heart attack*time		-0.05 (-0.21 - 0.11)
Hypertension*time		0.02 (-0.05 - 0.08)
Heart murmur*time		0.13 (0.00 - 0.26)
Intercept	65.22 (45.33 - 85.11)	53.15 (31.99 - 74.31)
Random effects (identity matrix)		
Intercept variance	132.94 (127.04 - 139.11)	127.29 (121.58 - 133.27)
AR1 Residuals by Frailty category		
variance		
Robust	27.24 (26.23 - 28.29)	27.01 (26.00 - 28.05)
Prefrail	34.58 (32.49 - 36.80)	33.85 (31.80 - 36.02)
Frail	43.00 (33.60 - 55.05)	44.42 (34.17 - 57.72)
rho		
Robust	0.63 (0.62 - 0.65)	0.63 (0.62 - 0.65)
Prefrail	0.67 (0.64 - 0.69)	0.66 (0.64 - 0.69)
Frail	0.66 (0.57 - 0.74)	0.66 (0.56 - 0.75)

Table SA6: Mixed effects models for HR recovery

Main effects	Model 1	Model 2
Period 1 10-20s	-43.78 (-49.74 - -37.83)	-27.96 (-34.38 - -21.54)
Period 2 20-30s	18.36 (12.48 - 24.24)	18.46 (12.13 - 24.80)
Period 3 30-110s	1.06 (-0.10 - 2.22)	1.44 (0.20 - 2.67)
Prefrail	0.92 (0.18 - 1.67)	0.98 (0.22 - 1.74)
Frail	2.09 (-0.32 - 4.50)	1.42 (-1.05 - 3.90)
Age	-0.66 (-1.22 - -0.10)	-0.63 (-1.18 - -0.09)
Age*age	0.00 (0.00 - 0.01)	0.00 (0.00 - 0.01)
Female	0.29 (-0.39 - 0.97)	-0.11 (-0.79 - 0.58)
Antidepressant		0.00 (-1.46 - 1.45)
Antihypertensive		-8.43 (-9.53 - -7.33)
BMI		-0.26 (-0.70 - 0.18)
BMI*BMI		0.01 (0.00 - 0.02)
Past smoker		-0.31 (-1.03 - 0.42)
Current smoker		0.83 (-0.18 - 1.83)
CES-D score		-0.03 (-0.09 - 0.03)
Diabetes		1.42 (0.03 - 2.81)
Stroke		-0.67 (-3.88 - 2.54)
Angina		-2.56 (-4.34 - -0.79)
Heart attack		-2.21 (-4.06 - -0.36)
Hypertension		0.14 (-0.63 - 0.91)
Heart murmur		-0.43 (-1.95 - 1.08)
Interactions 10-20s		
Prefrail*time	1.03 (0.78 - 1.29)	0.71 (0.44 - 0.98)
Frail*time	2.99 (2.22 - 3.76)	1.45 (0.61 - 2.29)
Age*time	0.91 (0.72 - 1.09)	0.86 (0.67 - 1.05)
Age*age*time	0.00 (-0.01 - 0.00)	0.00 (-0.01 - 0.00)
Female*time	-0.52 (-0.75 - -0.29)	-0.67 (-0.91 - -0.43)
Antidepressant*time		1.52 (1.01 - 2.03)
Antihypertensive*time		0.38 (-0.01 - 0.76)
BMI*time		-0.96 (-1.11 - -0.80)
BMI*BMI*time		0.01 (0.01 - 0.02)
Past smoker*time		0.37 (0.12 - 0.62)
Current smoker*time		2.40 (2.05 - 2.75)
CES-D score*time		0.01 (-0.01 - 0.03)
Diabetes*time		1.01 (0.53 - 1.50)
Stroke*time		0.23 (-0.91 - 1.37)
Angina*time		0.88 (0.25 - 1.50)
Heart attack*time		0.61 (-0.04 - 1.26)
Hypertension*time		1.10 (0.83 - 1.37)
Heart murmur*time		-0.26 (-0.79 - 0.27)
Interactions 20-30s		
Prefrail*time	-0.04 (-0.29 - 0.21)	0.04 (-0.23 - 0.30)
Frail*time	-0.78 (-1.55 - -0.01)	-0.73 (-1.56 - 0.10)
Age*time	-0.59 (-0.77 - -0.40)	-0.58 (-0.76 - -0.39)
Age*age*time	0.00 (0.00 - 0.01)	0.00 (0.00 - 0.01)
Female*time	0.13 (-0.09 - 0.36)	0.13 (-0.11 - 0.37)
Antidepressant*time		0.24 (-0.27 - 0.74)
Antihypertensive*time		0.32 (-0.06 - 0.70)
BMI*time		0.02 (-0.13 - 0.17)

BMI*BMI*time		0.00 (0.00 - 0.00)
Past smoker*time		0.03 (-0.22 - 0.27)
Current smoker*time		0.09 (-0.26 - 0.43)
CES-D score*time		-0.01 (-0.04 - 0.01)
Diabetes*time		0.41 (-0.07 - 0.90)
Stroke*time		0.08 (-1.04 - 1.21)
Angina*time		-0.68 (-1.29 - -0.06)
Heart attack*time		0.01 (-0.63 - 0.65)
Hypertension*time		-0.18 (-0.45 - 0.08)
Heart murmur*time		-0.54 (-1.06 - -0.02)
Interactions 30-110s		
Prefrail*time	-0.04 (-0.09 - 0.01)	-0.02 (-0.07 - 0.03)
Frail*time	-0.14 (-0.30 - 0.02)	-0.11 (-0.29 - 0.07)
Age*time	-0.02 (-0.05 - 0.02)	-0.01 (-0.04 - 0.03)
Age*age*time	0.00 (0.00 - 0.00)	0.00 (0.00 - 0.00)
Female*time	0.05 (0.00 - 0.09)	0.02 (-0.02 - 0.07)
Antidepressant*time		0.01 (-0.09 - 0.11)
Antihypertensive*time		-0.07 (-0.14 - 0.01)
BMI*time		-0.03 (-0.06 - 0.00)
BMI*BMI*time		0.00 (0.00 - 0.00)
Past smoker*time		-0.02 (-0.07 - 0.02)
Current smoker*time		-0.07 (-0.13 - 0.00)
CES-D score*time		0.00 (0.00 - 0.00)
Diabetes*time		-0.05 (-0.15 - 0.04)
Stroke*time		0.08 (-0.14 - 0.30)
Angina*time		-0.02 (-0.14 - 0.10)
Heart attack*time		0.06 (-0.07 - 0.18)
Hypertension*time		-0.03 (-0.08 - 0.03)
Heart murmur*time		-0.02 (-0.12 - 0.08)
Intercept	108.79 (91.05 - 126.53)	105.66 (87.23 - 124.09)
Random effects (identity matrix)		
Intercept variance	111.02 (106.20 - 116.05)	100.89 (96.46 - 105.52)
AR1 Residuals by Frailty category		
variance		
Robust	18.43 (17.77 - 19.12)	17.76 (17.14 - 18.41)
Prefrail	19.68 (18.71 - 20.69)	19.12 (18.19 - 20.09)
Frail	21.05 (16.70 - 26.53)	21.92 (17.13 - 28.05)
rho		
Robust	0.61 (0.60 - 0.63)	0.61 (0.59 - 0.62)
Prefrail	0.59 (0.57 - 0.61)	0.58 (0.56 - 0.61)
Frail	0.68 (0.59 - 0.75)	0.68 (0.59 - 0.76)

Table SA7: Mixed effects models for % BP & HR recovery by frailty criteria

Main effects	Systolic BP	Diastolic BP	Heart rate
Period 1 10-20s	-14.88 (-24.64 - -5.11)	6.27 (-4.77 - 17.30)	-47.02 (-56.84 - -37.20)
Period 2 20-30s	0.53 (-9.22 - 10.27)	3.03 (-7.92 - 13.98)	28.85 (19.13 - 38.57)
Period 3 30-110s	-0.59 (-2.94 - 1.76)	-0.52 (-2.83 - 1.78)	2.12 (0.17 - 4.07)
Slowness	-0.72 (-2.12 - 0.68)	1.89 (0.45 - 3.32)	-1.76 (-2.96 - -0.55)
Low Activity	0.69 (-0.36 - 1.73)	0.64 (-0.43 - 1.71)	0.26 (-0.63 - 1.16)
Weakness	0.09 (-1.23 - 1.40)	-0.22 (-1.57 - 1.12)	0.29 (-0.84 - 1.41)
Exhaustion	1.12 (-0.38 - 2.63)	0.73 (-0.81 - 2.27)	-0.64 (-1.93 - 0.65)
Weight loss	0.24 (-1.29 - 1.77)	0.30 (-1.27 - 1.87)	0.16 (-1.15 - 1.47)
Age	-0.58 (-1.16 - 0.01)	-0.71 (-1.31 - -0.11)	-0.59 (-1.10 - -0.09)
Age*age	0.00 (0.00 - 0.01)	0.00 (0.00 - 0.01)	0.00 (0.00 - 0.01)
Female	-1.11 (-1.85 - -0.37)	0.79 (0.03 - 1.55)	-1.29 (-1.92 - -0.65)
Antidepressant	-3.80 (-5.37 - -2.22)	-2.47 (-4.08 - -0.86)	-3.34 (-4.69 - -1.99)
Antihypertensive	-2.93 (-4.12 - -1.74)	-2.84 (-4.06 - -1.62)	-2.54 (-3.57 - -1.52)
BMI	0.84 (0.37 - 1.32)	0.99 (0.51 - 1.48)	0.76 (0.35 - 1.16)
BMI*BMI	-0.01 (-0.02 - 0.00)	-0.01 (-0.02 - 0.00)	-0.01 (-0.02 - 0.00)
Past smoker	0.45 (-0.33 - 1.23)	0.45 (-0.35 - 1.25)	0.00 (-0.67 - 0.68)
Current smoker	-0.03 (-1.12 - 1.05)	0.80 (-0.31 - 1.91)	-2.75 (-3.69 - -1.82)
CES-D score	-0.02 (-0.09 - 0.05)	0.03 (-0.04 - 0.10)	0.01 (-0.05 - 0.07)
Diabetes	1.50 (-0.01 - 3.00)	1.06 (-0.48 - 2.60)	-3.20 (-4.50 - -1.91)
Stroke	-1.85 (-5.31 - 1.62)	-3.21 (-6.76 - 0.34)	-0.11 (-3.08 - 2.87)
Angina	-2.88 (-4.79 - -0.96)	-3.85 (-5.81 - -1.90)	-1.34 (-2.98 - 0.30)
Heart attack	1.40 (-0.60 - 3.39)	0.61 (-1.43 - 2.65)	-1.04 (-2.75 - 0.67)
Hypertension	1.17 (0.33 - 2.00)	1.36 (0.51 - 2.21)	-2.11 (-2.83 - -1.40)
Heart murmur	-0.17 (-1.80 - 1.47)	-1.24 (-2.91 - 0.44)	0.45 (-0.95 - 1.86)
Interactions 10-20s			
Slowness*time	-2.33 (-3.02 - -1.64)	-3.82 (-4.59 - -3.04)	3.26 (2.57 - 3.96)
Low Activity*time	-0.48 (-0.99 - 0.04)	-0.56 (-1.14 - 0.02)	0.21 (-0.30 - 0.73)
Weakness*time	-0.41 (-1.05 - 0.24)	-0.26 (-0.98 - 0.47)	0.53 (-0.12 - 1.18)
Exhaustion*time	-0.76 (-1.50 - -0.02)	-0.62 (-1.45 - 0.22)	1.20 (0.46 - 1.95)
Weight loss*time	-0.61 (-1.37 - 0.14)	-1.11 (-1.96 - -0.26)	0.05 (-0.71 - 0.80)
Age*time	0.81 (0.52 - 1.10)	0.70 (0.37 - 1.02)	1.48 (1.19 - 1.77)
Age*age*time	-0.01 (-0.01 - -0.01)	-0.01 (-0.01 - -0.01)	-0.01 (-0.01 - -0.01)
Female*time	-1.65 (-2.01 - -1.28)	-3.19 (-3.60 - -2.78)	-0.87 (-1.24 - -0.50)
Antidepressant*time	-0.54 (-1.31 - 0.23)	-0.04 (-0.92 - 0.83)	2.30 (1.53 - 3.08)
Antihypertensive*time	-0.02 (-0.60 - 0.57)	0.14 (-0.52 - 0.80)	-0.14 (-0.73 - 0.45)
BMI*time	1.00 (0.77 - 1.23)	0.39 (0.13 - 0.65)	-1.53 (-1.77 - -1.30)
BMI*BMI*time	-0.01 (-0.02 - -0.01)	-0.01 (-0.01 - 0.00)	0.02 (0.02 - 0.03)
Past smoker*time	-0.52 (-0.90 - -0.14)	-0.94 (-1.38 - -0.51)	0.48 (0.09 - 0.86)
Current smoker*time	-2.02 (-2.55 - -1.49)	-1.97 (-2.57 - -1.36)	3.84 (3.30 - 4.38)
CES-D score*time	-0.03 (-0.07 - 0.00)	-0.07 (-0.10 - -0.03)	0.01 (-0.02 - 0.04)
Diabetes*time	-0.48 (-1.22 - 0.26)	-1.37 (-2.21 - -0.54)	1.49 (0.75 - 2.23)
Stroke*time	1.46 (-0.24 - 3.16)	3.59 (1.66 - 5.51)	-0.06 (-1.77 - 1.65)
Angina*time	1.55 (0.62 - 2.49)	1.86 (0.80 - 2.92)	1.24 (0.29 - 2.18)
Heart attack*time	0.90 (-0.07 - 1.88)	2.05 (0.94 - 3.15)	1.04 (0.06 - 2.02)
Hypertension*time	-2.16 (-2.57 - -1.75)	-2.36 (-2.82 - -1.89)	1.79 (1.38 - 2.20)
Heart murmur*time	0.89 (0.09 - 1.69)	-0.47 (-1.38 - 0.44)	-0.50 (-1.30 - 0.31)
Interactions 20-30s			
Slowness*time	0.96 (0.27 - 1.65)	0.70 (-0.07 - 1.47)	-0.25 (-0.94 - 0.43)
Low Activity*time	-0.45 (-0.96 - 0.06)	-0.64 (-1.21 - -0.06)	0.04 (-0.47 - 0.55)

Weakness*time	0.56 (-0.09 - 1.20)	0.66 (-0.07 - 1.38)	-0.39 (-1.03 - 0.26)
Exhaustion*time	-0.89 (-1.63 - -0.16)	-0.70 (-1.53 - 0.13)	0.47 (-0.26 - 1.21)
Weight loss*time	-0.74 (-1.49 - 0.01)	-0.92 (-1.76 - -0.07)	0.15 (-0.60 - 0.90)
Age*time	0.07 (-0.22 - 0.36)	0.19 (-0.13 - 0.51)	-0.90 (-1.19 - -0.62)
Age*age*time	0.00 (0.00 - 0.00)	0.00 (0.00 - 0.00)	0.01 (0.00 - 0.01)
Female*time	1.53 (1.16 - 1.89)	2.61 (2.20 - 3.02)	0.25 (-0.11 - 0.61)
Antidepressant*time	0.94 (0.17 - 1.71)	0.18 (-0.68 - 1.05)	0.26 (-0.51 - 1.03)
Antihypertensive*time	0.82 (0.24 - 1.41)	0.84 (0.18 - 1.49)	0.34 (-0.25 - 0.92)
BMI*time	-0.22 (-0.46 - 0.01)	-0.38 (-0.64 - -0.12)	0.02 (-0.21 - 0.25)
BMI*BMI*time	0.00 (0.00 - 0.01)	0.00 (0.00 - 0.01)	0.00 (0.00 - 0.00)
Past smoker*time	-0.21 (-0.59 - 0.17)	-0.33 (-0.76 - 0.10)	-0.03 (-0.41 - 0.35)
Current smoker*time	0.43 (-0.10 - 0.97)	-0.57 (-1.17 - 0.03)	0.16 (-0.37 - 0.69)
CES-D score*time	0.00 (-0.03 - 0.04)	0.00 (-0.04 - 0.04)	-0.03 (-0.07 - 0.00)
Diabetes*time	-1.03 (-1.77 - -0.29)	-1.10 (-1.93 - -0.27)	0.73 (-0.01 - 1.46)
Stroke*time	0.48 (-1.22 - 2.18)	-0.20 (-2.10 - 1.71)	0.17 (-1.52 - 1.86)
Angina*time	0.82 (-0.12 - 1.76)	1.28 (0.22 - 2.33)	-1.03 (-1.97 - -0.10)
Heart attack*time	-0.42 (-1.39 - 0.56)	-0.50 (-1.60 - 0.60)	-0.06 (-1.04 - 0.91)
Hypertension*time	0.73 (0.33 - 1.14)	0.73 (0.27 - 1.19)	-0.18 (-0.59 - 0.23)
Heart murmur*time	0.15 (-0.65 - 0.95)	0.33 (-0.57 - 1.23)	-0.78 (-1.58 - 0.02)
Interactions 30-110s			
Slowness*time	0.22 (0.06 - 0.39)	0.11 (-0.05 - 0.27)	-0.10 (-0.23 - 0.04)
Low Activity*time	0.06 (-0.06 - 0.18)	0.05 (-0.07 - 0.17)	0.02 (-0.08 - 0.12)
Weakness*time	0.05 (-0.11 - 0.20)	0.01 (-0.15 - 0.16)	-0.02 (-0.15 - 0.11)
Exhaustion*time	0.11 (-0.07 - 0.29)	0.12 (-0.05 - 0.30)	-0.09 (-0.24 - 0.06)
Weight loss*time	0.03 (-0.15 - 0.21)	0.05 (-0.13 - 0.23)	-0.01 (-0.16 - 0.14)
Age*time	0.03 (-0.04 - 0.10)	0.01 (-0.05 - 0.08)	-0.01 (-0.06 - 0.05)
Age*age*time	0.00 (0.00 - 0.00)	0.00 (0.00 - 0.00)	0.00 (0.00 - 0.00)
Female*time	0.04 (-0.05 - 0.13)	0.07 (-0.02 - 0.15)	0.02 (-0.05 - 0.10)
Antidepressant*time	0.14 (-0.04 - 0.33)	0.10 (-0.08 - 0.29)	0.02 (-0.13 - 0.18)
Antihypertensive*time	0.00 (-0.14 - 0.15)	0.05 (-0.09 - 0.19)	-0.10 (-0.21 - 0.02)
BMI*time	-0.09 (-0.14 - -0.03)	-0.05 (-0.11 - 0.00)	-0.04 (-0.09 - 0.00)
BMI*BMI*time	0.00 (0.00 - 0.00)	0.00 (0.00 - 0.00)	0.00 (0.00 - 0.00)
Past smoker*time	0.04 (-0.06 - 0.13)	0.05 (-0.04 - 0.14)	-0.04 (-0.12 - 0.03)
Current smoker*time	0.18 (0.05 - 0.30)	0.11 (-0.02 - 0.23)	-0.12 (-0.22 - -0.01)
CES-D score*time	0.00 (0.00 - 0.01)	0.01 (0.00 - 0.01)	0.00 (-0.01 - 0.01)
Diabetes*time	0.12 (-0.06 - 0.30)	0.10 (-0.07 - 0.28)	-0.08 (-0.22 - 0.07)
Stroke*time	-0.13 (-0.54 - 0.28)	-0.21 (-0.61 - 0.19)	0.14 (-0.20 - 0.48)
Angina*time	0.12 (-0.11 - 0.34)	0.05 (-0.17 - 0.27)	-0.03 (-0.22 - 0.16)
Heart attack*time	0.02 (-0.22 - 0.25)	-0.06 (-0.29 - 0.17)	0.08 (-0.12 - 0.27)
Hypertension*time	0.07 (-0.03 - 0.17)	0.04 (-0.06 - 0.13)	-0.05 (-0.13 - 0.03)
Heart murmur*time	0.12 (-0.08 - 0.31)	0.20 (0.01 - 0.39)	-0.03 (-0.19 - 0.13)
Intercept	83.69 (63.80 - 103.57)	78.80 (58.44 - 99.15)	142.09 (125.01 - 159.16)
Random effects (identity matrix)			
Intercept variance	69.64 (64.89 - 74.73)	82.84 (78.37 - 87.57)	57.40 (54.32 - 60.66)
AR1 Residuals			
variance			
	70.38 (67.05 - 73.87)	63.71 (61.56 - 65.93)	45.70 (44.29 - 47.16)
rho			
	0.76 (0.75 - 0.77)	0.66 (0.65 - 0.67)	0.63 (0.61 - 0.64)